Submission of Clinical Data Supporting Formulary Consideration of

AZOR™ (amlodipine and olmesartan medoxomil)
Daiichi Sankyo, Inc.

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AMCP Formulary Dossier

AZOR™ (amlodipine and olmesartan medoxomil)

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3.1. References

1 . PRODUCT INFORMATION

a. **Generic, Brand Name, Therapeutic Class:**
amlodipine and olmesartan medoxomil
AZOR™
Dihydropyridine Calcium Channel Blocker and Selective AT_1 subtype Angiotensin II Receptor Antagonist.

b. **Dosage Forms/National Drug Code (NDC)/Cost:**
AZOR™ tablets are differentiated by tablet color/size and are debossed with an individual product tablet code on one side. AZOR™ tablets are supplied for oral administration in the following strength and package configurations listed in Table 1.

Table 1: Tablets are supplied as follows (includes NDC codes and WAC Cost):

Tablet Strength (amlodipine equivalent/olmesartan medoxomil) mg	Package Configuration	NDC#	WAC Tablet Price	WAC Package Price
5/20 mg	Bottle of 30 Bottle of 90 10 blisters of 10 Bottle of 1000	65597-110-30 65597-110-90 65597-110-10 65597-110-11	$2.13 $2.13 $2.13	$63.90 $191.70 $213.00
10/20 mg	Bottle of 30 Bottle of 90 10 blisters of 10 Bottle of 1000	65597-111-30 65597-111-90 65597-111-10 65597-111-11	$2.41 $2.41 $2.41	$72.30 $216.90 $241.00
5/40 mg	Bottle of 30 Bottle of 90 10 blisters of 10 Bottle of 1000	65597-112-30 65597-112-90 65597-112-10 65597-112-11	$2.70 $2.70 $2.70	$81.00 $243.00 $270.00
10/40 mg	Bottle of 30 Bottle of 90 10 blisters of 10 Bottle of 1000	65597-113-30 65597-113-90 65597-113-10 65597-113-11	$3.06 $3.06 $3.06	$91.80 $275.40 $306.00

c. **Product Labeling:** Enclosed in binder

d. **AHFS Drug Classification:**
Amlodipine - 24:04
Olmesartan – 24:08

e. **FDA Approved Indication:** AZOR™ is indicated for the treatment of hypertension, alone or with other antihypertensive agents. This fixed combination drug is not indicated for the initial therapy of hypertension
Date of approval: September 26, 2007.

e. Pharmacology:

AZOR™ is a combination of two antihypertensive drugs: a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker), amlodipine besylate, and an angiotensin II receptor blocker, olmesartan medoxomil. The amlodipine component of AZOR™ inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle, and the olmesartan medoxomil component of AZOR™ blocks the vasoconstrictor effects of angiotension II.

Amlodipine. Experimental data suggests that amlodipine binds to both dihydropyridine and nondihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Amlodipine inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Negative inotropic effects can be detected *in vitro* but such effects have not been seen in intact animals at therapeutic doses. Serum calcium concentration is not affected by amlodipine. Within the physiologic pH range, amlodipine is an ionized compound (pKa=8.6), and its kinetic interaction with the calcium channel receptor is characterized by a gradual rate of association and dissociation with the receptor binding site, resulting in a gradual onset of effect.

Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure.

Olmesartan medoxomil. Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation and renal reabsorption of sodium. Olmesartan blocks the vasoconstrictor effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 receptor in vascular smooth muscle. Its action is, therefore, independent of the pathways for angiotensin II synthesis.

An AT_2 receptor is found also in many tissues, but this receptor is not known to be associated with cardiovascular homeostasis. Olmesartan has more than a 12,500-fold greater affinity for the AT_1 receptor than for the AT_2 receptor.

Blockade of the renin-angiotensin system with ACE inhibitors, which inhibit the biosynthesis of angiotensin II from angiotensin I, is a mechanism of many drugs used to treat hypertension. ACE inhibitors also inhibit the degradation of bradykinin, a reaction also catalyzed by ACE. Because olmesartan does not inhibit ACE (kininase II), it does not affect the response to bradykinin. Whether this difference has clinical relevance is not yet known.

Blockade of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and circulating angiotensin II levels do not overcome the effect of olmesartan on blood pressure.

f. Pharmacokinetics:

The pharmacokinetics of amlodipine and olmesartan medoxomil from AZOR™ are equivalent to the pharmacokinetics of amlodipine and olmesartan medoxomil when administered separately. The bioavailability of both components is well below 100%, but neither component is affected by food. The effective half-lives of amlodipine (45±11 hours) and olmesartan (7±1 hours) result in a 2- to 3- fold accumulation for amlodipine and negligible accumulation for olmesartan with once-daily dosing.

Amlodipine. After oral administration of therapeutic doses of amlodipine, absorption produces peak plasma concentrations between 6 and 12 hours. Absolute bioavailability is estimated as between 64% and 90%.

Olmesartan medoxomil. Olmesartan medoxomil is rapidly and completely bioactivated by ester hydrolysis to olmesartan during absorption from the gastrointestinal tract. The absolute bioavailability of olmesartan medoxomil is approximately 26%. After oral administration, the peak plasma concentration (C_{max}) of olmesartan is reached after 1 to 2 hours. Food does not affect the bioavailability of olmesartan medoxomil.

Distribution
Amlodipine. Ex vivo studies have shown that approximately 93% of the circulating drug is bound to plasma proteins in hypertensive patients. Steady-state plasma levels of amlodipine are reached after 7 to 8 days of consecutive daily dosing.

Olmesartan medoxomil. The volume of distribution of olmesartan is approximately 17 L. Olmesartan is highly bound to plasma proteins (99%) and does not penetrate red blood cells. The protein binding is constant at plasma olmesartan concentrations well above the range achieved with recommended doses.

In rats, olmesartan crossed the blood-brain barrier poorly, if at all. Olmesartan passed across the placental barrier in rats and was distributed to the fetus. Olmesartan was distributed to milk at low levels in rats.

Metabolism and Excretion:

Amlodipine. Amlodipine is extensively (about 90%) converted to inactive metabolites via hepatic metabolism. Elimination from the plasma is biphasic with a terminal elimination half-life of about 30 to 50 hours. Ten percent of the parent compound and 60% of the metabolites are excreted in the urine.

Olmesartan medoxomil. Following the rapid and complete conversion of olmesartan medoxomil to olmesartan during absorption, there is virtually no further metabolism of olmesartan. Total plasma clearance of olmesartan is 1.3 L/h with a renal clearance of 0.6 L/h. Approximately 35% to 50% of the absorbed dose is recovered in urine while the remainder is eliminated in feces via the bile.

Olmesartan appears to be eliminated in a biphasic manner with a terminal elimination half-life of approximately 13 hours. Olmesartan shows linear pharmacokinetics following single oral doses of up to 320 mg and multiple oral doses of up to 80 mg. Steady-state levels of olmesartan are achieved within 3 to 5 days and no accumulation in plasma occurs with once-daily dosing.

g. Contraindications: None.

h. Warnings and Precautions: The adverse reactions of AZOR™ are generally related to those of each of its components.

Fetal/Neonatal Morbidity and Mortality

Olmesartan medoxomil. Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. There have been several dozen cases reported in the world literature of patients who were taking angiotensin converting enzyme inhibitors. When pregnancy is detected, AZOR™ should be discontinued as soon as possible.

During the second and third trimesters of pregnancy, these drugs have been associated with fetal injury that includes hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug.

These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should have the patient discontinue the use of AZOR™ as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to a drug acting on the renin-angiotensin system will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses and serial ultrasound examinations should be performed to assess the intra-amniotic environment.

If oligohydramnios is observed, AZOR™ should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function.

No teratogenic effects were observed when olmesartan medoxomil was administered to pregnant rats at oral doses up to 1000 mg/kg/day (240 times the maximum recommended human dose (MRHD) on a mg/m^2 basis) or pregnant rabbits at oral doses up to 1 mg/kg/day (half the MRHD on a mg/m^2 basis; higher doses could not be evaluated for effects on fetal development as they were lethal to the dose). In rats, significant decreases in pup birth weight and weight gain were observed at doses ≥1.6 mg/kg/day, and delays in developmental milestones (delayed separation of ear auricular, eruption of lower incisors, appearance of abdominal hair, descent of testes, and separation of eyelids) and dose-dependent increase in the incidence of dilation of the renal pelvis were observed at doses ≥8 mg/kg/day. The no observed effect dose for developmental toxicity in rats is 0.3 mg/kg/day, about one-tenth the MRHD of 40 mg/day.

Hypotension in Volume- or Salt-Depleted Patients

Olmesartan medoxomil*.* Symptomatic hypotension may occur after initiation of treatment with olmesartan medoxomil. Patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients (e.g., those being treated with high doses of diuretics) may be particularly vulnerable. Treatment with AZOR™ should start under close medical supervision. If hypotension does occur, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

Vasodilation

Amlodipine*.* Since the vasodilation attributable to amlodipine in AZOR™ is gradual in onset, acute hypotension has rarely been reported after oral administration. Nonetheless, caution, as with any other peripheral vasodilator, should be exercised when administering AZOR™, particularly in patients with severe aortic stenosis.

Patients with Severe Obstructive Coronary Artery Disease

Patients, particularly those with severe obstructive coronary artery disease, may develop increased frequency, duration, or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase. The mechanism of this effect has not been elucidated.

Patients with Congestive Heart Failure

Amlodipine*.* In general, calcium channel blockers should be used with caution in patients with heart failure. Amlodipine (5-10 mg per day) has been studied in a placebo-controlled trial of 1153 patients with NYHA (New York Heart Association) Class III or IV heart failure on stable doses of ACE inhibitor, digoxin, and diuretics. Follow-up was at least 6 months, with a mean of about 14 months. There was no overall adverse effect on survival or cardiac morbidity (as defined by life-threatening arrhythmia, acute myocardial infarction, or hospitalization for worsened heart failure). Amlodipine has been compared to placebo in four 8-12 week studies of patients with NYHA class II/III heart failure, involving a total of 697 patients. In these studies, there was no evidence of worsening of heart failure based on measures of exercise tolerance, NYHA classification, symptoms, or left ventricular ejection fraction (LVEF).

Patients with Impaired Renal Function

Olmesartan medoxomil*.* Changes in renal function may be anticipated in susceptible individuals treated with olmesartan medoxomil as a consequence of inhibiting the renin-angiotensin aldosterone system. In patients whose renal function may depend upon the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure), treatment with angiotensin converting enzyme inhibitors and angiotensin receptor antagonists has been associated with oliguria or progressive azotemia and (rarely) with acute renal failure and/or death. Similar effects may occur in patients treated with AZOR™ due to the olmesartan medoxomil component *[See Clinical Pharmacology (12.3)]*.

In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen (BUN) have been reported. There has been no long-term use of olmesartan medoxomil in patients with unilateral or bilateral renal artery stenosis, but similar effects would be expected with AZOR™ because of the olmesartan medoxomil component.

Patients with Hepatic Impairment

Amlodipine*.* Since amlodipine is extensively metabolized by the liver and the plasma elimination half-life ($t_{1/2}$) is 56 hours in patients with severely impaired hepatic function, caution should be exercised when administering AZOR™ to patients with severe hepatic impairment.

i. Adverse Reactions:

Clinical Trials Experience
Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

AZOR™
The data described below reflect exposure to AZOR™ in more than 1600 patients including more than 1000 exposed for at least 6 months and more than 700 exposed for 1 year. AZOR™ was studied in one placebo-controlled factorial trial (see Section 14.1). The population had a mean age of 54 years and included approximately 55% males. Seventy-one percent were Caucasian and 25% were Black. Patients received doses ranging from 5/20 mg to 10/40 mg orally once daily.

The overall incidence of adverse reactions on therapy with AZOR™ was similar to that seen with corresponding doses of the individual components of AZOR™, and to placebo. The reported adverse reactions were generally mild and seldom led to discontinuation of treatment (2.6% for AZOR™ and 6.8% for placebo).

Edema
Edema is a known, dose-dependent adverse effect of amlodipine but not of olmesartan medoxomil.

The placebo-subtracted incidence of edema during the 8-week, randomized, double-blind treatment period was highest with amlodipine 10 mg monotherapy. The incidence was significantly reduced when 20 mg or 40 mg of olmesartan medoxomil was added to the 10 mg amlodipine dose.

Table 2: Placebo-Subtracted Incidence of Edema during the Double-Blind Treatment Period

			Olmesartan Medoxomil	
		Placebo	**20 mg**	**40 mg**
	Placebo	0%*	(-2.4%)	6.2%
Amlodipine	**5 mg**	0.7%	5.7%	6.2%
	10 mg	24.5%	13.3%	11.2%
*12.3%=actual placebo incidence				

Across all treatment groups, the frequency of edema was generally higher in women than men, as has been observed in previous studies of amlodipine.

Adverse reactions seen at lower rates during the double-blind period also occurred in the patients treated with AZOR™ at about the same or greater incidence as in patients receiving placebo. These included hypotension, orthostatic hypotension, rash, pruritus, palpitation, urinary frequency, and nocturia.

The adverse event profile obtained from 44 weeks of open-label combination therapy with amlodipine plus olmesartan medoxomil was similar to that observed during the 8-week, double-blind, placebo-controlled period.

Amlodipine
Amlodipine has been evaluated for safety in more than 11,000 patients in U.S. and foreign clinical trials. Most adverse reactions reported during therapy with amlodipine were of mild or moderate severity. In controlled clinical trials directly comparing amlodipine (N=1730) in doses up to 10 mg to placebo (N=1250), discontinuation of amlodipine due to adverse reactions was required in only about 1.5% of amlodipine-treated patients and about 1% of placebo-treated patients. The most common side effects were headache and edema. The incidence (%) of dose-related side effects was as follows:

Table 3: Incidence (%) of dose-related side effects for amlodipine

Adverse Event	Placebo N=520	2.5 mg N=275	5.0 mg N=296	10.0 mg N=268
Edema	0.6	1.8	3.0	10.8
Dizziness	1.5	1.1	3.4	3.4
Flushing	0.0	0.7	1.4	2.5
Palpitation	0.5	0.7	1.4	4.5

For several adverse experiences that appear to be drug- and dose-related, there was a greater incidence in women than men associated with amlodipine treatment as shown in the following table:

Table 4: Incidence of drug- and dose-related side effects in women and men for amlodipine

Adverse Event	Placebo		Amlodipine	
	Male=% (N=914)	Female=% (N=336)	Male=% (N=1218)	Female=% (N=512)
Edema	1.4	5.1	5.6	14.5
Flushing	0.3	0.9	1.5	4.5
Palpitation	0.9	0.9	1.4	3.3
Somnolence	0.8	0.3	1.3	1.6

Olmesartan medoxomil
Olmesartan medoxomil has been evaluated for safety in more than 3825 patients/subjects, including more than 3275 patients treated for hypertension in controlled trials. This experience included about 900 patients treated for at least 6 months and more than 525 for at least 1 year. Treatment with olmesartan medoxomil was well tolerated, with an incidence of adverse events similar to that seen with placebo. Events were generally mild, transient, and without relationship to the dose of olmesartan medoxomil.

The overall frequency of adverse events was not dose-related. Analysis of gender, age, and race groups demonstrated no differences between olmesartan medoxomil- and placebo-treated patients. The rate of withdrawals due to adverse events in all trials of hypertensive patients was 2.4% (i.e., 79/3278) of patients treated with olmesartan medoxomil and 2.7% (i.e., 32/1179) of control patients. In placebo-controlled trials, the only adverse event that occurred in more than 1% of patients treated with olmesartan medoxomil and at a higher incidence in olmesartan medoxomil treated patients vs. placebo was dizziness (3% vs 1%).

j. Drug Interactions:

Drug Interactions with AZOR™
The pharmacokinetics of amlodipine and olmesartan medoxomil are not altered when the drugs are co-administered.

No drug interaction studies have been conducted with AZOR™ and other drugs, although studies have been conducted with the individual amlodipine and olmesartan medoxomil components of AZOR™, as described below, and no significant drug interactions have been observed.

Drug Interactions with Amlodipine
In vitro data indicate that amlodipine has no effect on the human plasma protein binding of digoxin, phenytoin, warfarin, and indomethacin.

Effect of Other Agents on Amlodipine

Cimetidine: Co-administration of amlodipine with cimetidine did not alter the pharmacokinetics of amlodipine.
Grapefruit juice: Co-administration of 240 mL of grapefruit juice with a single oral dose of amlodipine 10 mg in 20 healthy volunteers had no significant effect on the pharmacokinetics of amlodipine.
Maalox® (antacid): Co-administration of the antacid Maalox® with a single dose of amlodipine had no significant effect on the pharmacokinetics of amlodipine.
Sildenafil: A single 100 mg dose of sildenafil in subjects with essential hypertension had no effect on the pharmacokinetic parameters of amlodipine. When amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

Effect of Amlodipine on Other Agents

Atorvastatin: Co-administration of multiple 10 mg doses of amlodipine with 80 mg of atorvastatin resulted in no significant change in the steady state pharmacokinetic parameters of atorvastatin.
Digoxin: Co-administration of amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers.
Ethanol (alcohol): Single and multiple 10 mg doses of amlodipine had no significant effect on the pharmacokinetics of ethanol.
Warfarin: Co-administration of amlodipine with warfarin did not change the warfarin prothrombin response time.

In clinical trials, amlodipine has been safely administered with thiazide diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs.

Drug Interactions with Olmesartan Medoxomil
No significant drug interactions were reported in studies in which olmesartan medoxomil was co-administered with digoxin or warfarin in healthy volunteers.

The bioavailability of olmesartan medoxomil was not significantly altered by the co-administration of antacids [Al(OH)3/Mg(OH)2].

Olmesartan medoxomil is not metabolized by the cytochrome P450 system and has no effects on P450 enzymes; thus, interactions with drugs that inhibit, induce, or are metabolized by those enzymes are not expected.

k. Dosage and Administration

AZOR™ may be substituted for its individually titrated components for patients on amlodipine and olmesartan medoxomil. AZOR™ may also be given with increased amounts of amlodipine, olmesartan medoxomil, or both, as needed.

AZOR™ may be used as add-on therapy for patients not adequately controlled on amlodipine or olmesartan medoxomil. Dosage may be increased after 2 weeks to a maximum dose of 10/40 mg once daily, usually by increasing one component at a time but both components can be raised to achieve more rapid control. Maximum antihypertensive effects are attained within 2 weeks after a change in dose. AZOR™ may be administered with other antihypertensive agents.

The side effects of olmesartan medoxomil are generally rare and apparently independent of dose. Those of amlodipine are generally dose-dependent (mostly edema).

AZOR™ may be taken with or without food.

l. Comparative Pharmacokinetic/Pharmacologic Profiles of Available ARBs

Table 5: Comparative Pharmacokinetic/Pharmacologic Profiles of Available ARBs

	Olmesartan medoxomil	**Candesartan cilexetil[1]**	**Eprosartan[2]**	**Irbesartan[3]**	**Losartan potassium[4]**	**Telmisartan[5]**	**Valsartan[6]**
Prodrug	Yes	Yes	No	No	Yes	No	No
AT_1 Receptor Affinity	IC_{50} 5-6 nmol/L	K_i 0.6	IC_{50} 1-4 nmol/L	IC_{50} 1.3 nmol/L	IC_{50} 20 nmol/L	K_i 3.7	IC_{50} 2.7 nmol/L
Maximal Onset (wk)	2	2-4	3	2	2-3	3	2
Peak (hr)	1-2	3-4	3	1.5-2	3-4	.5-1	2-4
BA (%)		15	13	60-80	33	42-58	25
Food Effect (↓AUC %)	_____	_____	25	_____	10	6	40-50
$T_{1/2}$ (hr)	13	9	5-9	12-20	2	24	6
Protein Binding (%)	99	>99	98	90	99	>99.5	>95
P 450 Metabolism	No	No	No	Yes	Yes	No	Uncertain
Drug Interactions	No	No	No	No	Rifampin, fluconazole	Digoxin	No
Fecal Elimination (%)	50-65	67	90	80	60	98	83
Urinary Elimination (%)	35-50	33	7	20	35	<1	13
Trough to Peak Ratio	52-79	80	67	>60	58-78	>97	69-76
Dosages Available (mg)	5, 20, 40	4,8,16,32	400,600	75, 150, 300	25, 50, 100	20, 40, 80	40, 80, 160, 320
Dosing Frequency	QD	QD/BID	QD/BID	QD	QD/BID	QD	QD

BA=bioavailability

K_i=inhibition constant

[1]Atacand® package insert. Wayne, PA: AstraZeneca Pharmaceuticals; 2005.

[2]Teveten® package insert. Bridgewater, NJ: Biovail Pharmaceuticals, Inc.; 2004.

[3]Avapro® package insert. Princeton, NJ: Bristol-Myers Squibb Company; 2004.

[4]Cozaar® package insert. West Point, PA: Merck & Co.; 2004.

[5]Micardis® package insert. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals; 2003.

[6]Diovan® package insert. East Hanover, NJ: Novartis Pharmaceuticals Corp.; 2005.

n. Comparative Pharmacokinetic/Pharmacologic Profiles of Available Dihydropridine CCBs

Table 6: Comparative Pharmacokinetic/Pharmacologic Profiles of Available Dihydropyridine CCBs

	Amlodipine besylate[1]	Felodipine[2]	Isradipine[3]	Nicardipine hydrochloride[4]	Nifedipine[5]	Nisoldipine[6]
Peak (hr)	6-12	2.5-5	8-10	1-4	6	6-12
BA (%)	64-90	20	15-24	35	86	5
Food Effect (↓AUC%)	————	————	25	25	————	25
T½ (hr)	30-50	11-16	8	8.6	2	7-12
Protein Binding (%)	93	>99	95	>95	92-98	>99
P450 Metabolism	No	Yes - CYP3A4	No	No	Yes	Yes – CYP3A4
Drug Interactions	No significant effects by: cimetidine, grapefruit juice, Maalox (antacid), sildenafil, atorvastatin, digoxin, ethanol (alcohol), warfarin, thiazide diuretics, beta-blockers, ACEIs, long-acting nitrates, sublingual nitroglycerin, NSAIDs, antibiotics, and oral hypoglycemic agents	Increased effect with: CYP3A4 inhibitors (eg, Itraconazole, erythromycin, grapefruit juice, cimetidine) Increases effect of: tacrolimus Decreased effect: anticonvulsants No significant effects by: Beta-blockers, digoxin, indomethacin, spironolactone	Noted interaction: Fentanyl anesthesia with concomitant use of a beta-blocker may cause severe hypotension Increases effect of: propanolol No significant effects by: nitroglycerin, HCTZ, digoxin	Noted interaction: Fentanyl anesthesia with concomitant use of a beta-blocker may cause severe hypotension Increased effect with: cimetidine Increases effect of: cyclosporine No significant effects by: beta-blockers, digoxin, furosemide, propanolol, dipyridamole, warfarin, quinidine, naproxen	Increased effect with: cimetidine Increases effect of: digitalis No significant effects by: beta-blockers, long-acting nitrates, coumarin anticoagulants	Increased effect with: cimetidine Decreased effect with: CYP3A4 inducers, phenytoin, quinidine No significant effects by: ranitidine, beta-blockers (eg, atenolol, propanolol), digoxin, warfarin
Incidence of Edema (%)	**Dose-Related:*** **2.5 mg:** 1.8 **5.0 mg:** 3 **10 mg:** 10.8 **Placebo:** 0.6	**Dose-Related: *†** **2.5 mg:** 2.0 **5.0 mg:** 8.8 **10 mg:** 17.4 **Placebo:** 3.3	**Dose-Related:** **5 mg:** 8.9 **10 mg:** 12.7 **15 mg:** 15.9 **20 mg:** 35.9 **Placebo:** 3.6	**Dose-Related*†** **Cardene® SR(exact doses not listed):** 5.9 **Placebo:** 1.4	**Dose-Related*†** **Low Dose:** 10 **Highest Dose (180 mg):†** 30	**Dose-Related: *†** **10 mg:** 7 **20 mg:** 15 **30 mg:** 20 **40 mg:** 27 **60 mg:** 29 **Placebo:** 10
Fecal Elimination (%)	Not listed	10	25-30	35	20-40	Not listed
Urinary Elimination (%)	10% parent compound; 60% metabolites	70	60-65	60	60-80	60-80
Trough:Peak Ratio	Not listed	40-50	76	Not listed	Not listed	70-100
Dosages Available (mg)	2.5, 5, 10	2.5, 5, 10	5, 10	30, 45, 60	30, 60, 90	10, 20, 30, 40
Dosing Frequency	Daily	Daily	Daily	Twice Daily	Daily	Daily

BA = bioavailability
* Results are from pooled data

† Results presented as therapy without regard to causality

[1] Norvasc® package insert. New York, NY: Pfizer Inc,; 2005

[2] Plendil® package insert. Wilmington, DE: AstraZeneca LP; 2003

[3] DynaCirc CR® package insert. Liberty Corner, NJ: Reliant Pharmaceuticals, Inc.; 2005

[4] Cardene® SR package insert. Nutley, NJ: Roche Pharmaceuticals; 2000

[5] Procardia XL® package insert. New York, NY: Pfizer Inc.; 2003

[6] Sular® package insert. Atlanta, GA: Sciele Pharma, Inc.; 2006

o. Comparative Pharmacokinetic/Pharmacologic Profiles of Fixed Dose Amlodipine Combination Products

Table 7: Comparative Pharmacokinetic/Pharmacologic Profiles of Fixed Dose Amlodipine Combination Products

	AZOR™ (amlodipine and olmesartan medoxomil)[1]	**Exforge® (amlodipine and valsartan)[2]**	**Lotrel® (amlodipine besylate/benazepril HCl)[3]**
Indications	Hypertension, alone or with other antihypertensive agents Not indicated for initial therapy	Hypertension Not indicated for initial therapy	Hypertension Not indicated for initial therapy
BA (%)	**Amlodipine**: 64-90 **Olmesartan**: 26	**Amlodipine**: 64-90 **Valsartan**: 25% (range: 10-35)	**Amlodipine**: 64-90 **Benazepril**: ≥37
T½ (hr)	**Amlodipine**: 30-50 **Olmesartan**: 13 (elimination)	**Amlodipine**: 30-50 **Valsartan**: 6 (elimination)	**Amlodipine**: approximately 2 days (elimination) **Benazepril**: 10-11 (elimination)
Time to Peak Plasma Concentrations (T_{max}) (hr)	**Amlodipine**: 6-12 **Olmesartan**: 1-2	**Amlodipine**: 6-12 **Valsartan**: 2-4	**Amlodipine**: 6-12 **Benazepril**: 1.5-4
Protein Binding (%)	**Amlodipine**: 93 **Olmesartan**: 99	**Amlodipine**: 93 **Valsartan**: 95	**Amlodipine**: 93 **Benazepril**: Not specified
Volume of Distribution (L)	**Amlodipine**: 21 **Olmesartan**: 17	**Amlodipine**: 21 **Valsartan**: 17	**Amlodipine**: 21 **Benazeprilat**: 0.7
Metabolism	**Amlodipine**: extensively (about 90%) converted to inactive metabolites via hepatic metabolism **Olmesartan**: following the rapid and complete conversion of olmesartan medoxomil to olmesartan during absorption, there is virtually no further metabolism of olmesartan	No CYP450 Metabolism **Amlodipine**: extensively (about 90%) converted to inactive metabolites via hepatic metabolism **Valsartan**: primary metabolite is valeryl 4-hydroxy valsartan and accounts for 9% of dose	**Amlodipine**: extensively metabolized in the liver **Benazepril**: the metabolism of benazepril to benazeprilat is almost complete
Elimination	**Amlodipine**: 10% of the parent compound and 60% of the metabolites are excreted in the urine **Olmesartan**: Approximately 35% to 50% of the absorbed dose is recovered in urine while the remainder is eliminated in feces via the bile	**Amlodipine**: 10% of parent compound and 60% of the metabolites excreted in the urine **Valsartan**: when administered as an oral solution, is primarily recovered in feces (about 83% of dose) and urine (about 13% of dose)	**Amlodipine**: 10% of the parent compound and 60% of the metabolites excreted in the urine **Benazepril**: only trace amounts of an administered dose of benazepril can be recovered unchanged in the urine; about 20% of the dose is excreted as benazeprilat, 8% as benazeprilat glucuronide, and 4% as benazepril glucuronide

Continued – Table 7 - Comparative Pharmacokinetic/Pharmacologic Profiles of Fixed Dose Amlodipine Combination Products

	AZOR™ (amlodipine and olmesartan medoxomil)[1]	Exforge® (amlodipine and valsartan)[2]	Lotrel® (amlodipine besylate/benazepril HCl)[3]
Drug Interactions	No drug interaction studies have been conducted with AZOR and other drugs, although studies have been conducted with the individual amlodipine and olmesartan components, as described below: **Amlodipine**: No significant effects with/by: cimetidine, grapefruit juice, sildenafil, atorvastatin, digoxin, ethanol (alcohol), warfarin In clinical trials, amlodipine has been safely administered with thiazide diuretics, beta blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs **Olmesartan**: No significant drug interactions were reported in studies in which olmesartan was coadministered with digoxin or warfarin in healthy volunteers. Olmesartan medoxomil is not metabolized by the cytochrome P450 system; thus, interactions with drugs that inhibit, induce, or are metabolized by those enzymes are not expected	No drug interaction studies have been conducted with Exforge and other drugs, although studies have been conducted with the individual amlodipine and valsartan components, as described below: **Amlodipine**: No significant effects with/by: cimetidine, grapefruit juice, Maalox (antacid), sildenafil, atorvastatin, digoxin, ethanol (alcohol), warfarin, thiazide diuretics, beta-blockers, ACEIs, long-acting nitrates, sublingual nitroglycerin, NSAIDs, antibiotics, and oral hypoglycemic agents. **Valsartan**: No significant effects with/by: amlodipine, atenolol, cimetidine, digoxin, furosemide, glyburide, hydrochlorothiazide, indomethacin, or warfarin. Concomitant use of potassium sparing diuretics (e.g., spirinolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium and serum creatinine in heart failure patients, as with other drugs that block angiotensin II or its effects.	Patients receiving concomitant diuretic therapy may occasionally experience an excessive reduction in blood pressure after initiation of therapy with Lotrel. **Amlodipine**: safely administered with thiazide diuretics, beta blockers, ACE inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, nonsteroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs. **Benazepril**: safe to administer and use concomitantly with oral anticoagulants, beta-adrenergic blocking agents, calcium-blocking agents, cimetidine, diuretics, digoxin, hydralazine, and naproxen. Increased serum lithium levels and symptoms of lithium toxicity have been reported – coadminister with caution and monitor serum lithium frequently. Benazepril may attenuate potassium loss caused by thiazide diuretics. Potassium-sparing diuretics (spirinolactone, amiloride, triamterene, and others) or potassium supplements can increase the risk of hyperkalemia – coadminister with caution and monitor serum potassium frequently

Continued – Table 7: Comparative Pharmacokinetic/Pharmacologic Profiles of Fixed Dose Amlodipine Combination Products

<table>
<tr><th></th><th>AZOR™ (amlodipine and olmesartan medoxomil)[1]</th><th>Exforge® (amlodipine and valsartan)[2]</th><th>Lotrel® (amlodipine besylate/benazepril HCl)[3]</th></tr>
<tr><td>Adverse Reactions</td><td>Edema is a known, dose-dependent adverse effect of amlodipine but not of olmesartan medoxomil.
The placebo-subtracted incidence of edema during the 8-week, randomized, double-blind treatment period was highest with amlodipine 10 mg monotherapy. The incidence was significantly reduced when 20 mg or 40 mg of olmesartan medoxomil was added to the 10 mg amlodipine dose.

<table><tr><td colspan="2"></td><td>Olmesartan Medoxomil</td><td></td><td></td></tr><tr><td colspan="2"></td><td>Placebo</td><td>20 mg</td><td>40 mg</td></tr><tr><td>Amlodipine</td><td>Placebo</td><td>0%*</td><td>(-2.4%)</td><td>6.2%</td></tr><tr><td></td><td>5 mg</td><td>0.7%</td><td>5.7%</td><td>6.2%</td></tr><tr><td></td><td>10 mg</td><td>24.5%</td><td>13.3%</td><td>11.2%</td></tr><tr><td colspan="5">*12.3% = actual placebo incidence</td></tr></table>
Adverse reactions seen at lower rates during the double-blind period also occurred in the patients treated with AZOR™ at about the same or greater incidence as in patients receiving placebo.
These included hypotension, orthostatic hypotension, rash, pruritus, palpitation, urinary frequency, and nocturia.</td><td>Incidence of AEs in ≥2% patients and more frequent than in placebo patients:

Peripheral edema (5.4%)
Nasopharyngitis (4.3%)
Upper respiratory tract infection (2.9%)
Dizziness (2.1%)</td><td>Incidence of AEs in ≥1% of patients considered possibly or probably related to study drug and more frequent than in placebo patients:

Cough (3.3%)
Headache (2.2%)
Edema (2.1%)
Dizziness (1.3%)</td></tr>
<tr><td>Dosages Available (mg)</td><td>5/20, 5/40, 10/20, 10/40 combination tablets</td><td>5/160, 10/160, 5/320, and 10/320 combination tablets</td><td>2.5/10, 5/10, 5/20, 5/40, 10/20, 10/40 combination tablets</td></tr>
<tr><td>Adult Dosing Frequency</td><td>Hypertension: Range:
5/20 mg daily up to a maximum dose of 10/40 mg daily</td><td>Hypertension: Range: 5/160 mg daily up to a maximum dose of 10/320 mg daily

For convenience, patients receiving amlodipine and valsartan from separate tablets may instead wish to receive tablets of Exforge® containing the same component doses</td><td>Hypertension: Range: 2.5/10 mg daily up to a maximum dose of 10/40 mg daily

For convenience, patients receiving amlodipine and benazepril from separate tablets may instead wish to receive tablets of Lotrel® containing the same component doses</td></tr>
</table>

BA = bioavailability

[1] AZOR package insert. Parsippany, NJ: Daiichi Sankyo, Inc.; 2007
[2] Exforge package insert. East Hanover, NJ: Novartis Pharmaceuticals; 2007
[3] Lotrel package insert. East Hanover, NJ: Novartis Pharmaceuticals; 2007

1.2 PLACE OF THE PRODUCT IN THERAPY

1.2.1 DISEASE DESCRIPTION: HYPERTENSION

a. Epidemiology and Clinical Aspects of Hypertension

Hypertension is a major cardiovascular risk factor that directly contributes to myocardial infarction (MI), cerebrovascular accidents, congestive heart failure (CHF), peripheral arterial insufficiency, and premature mortality. Optimal and cost-effective management of the condition depends on careful diagnosis, treatment minimization, optimized adherence, cost effective selection of tests and treatments, and practice efficiency.

Cardiovascular disease has been the dominant cause of death in the United States for over 50 years. About 12 million Americans currently have coronary heart disease. Another 4 million have had a stroke (Cooper, 2000). Heart disease and stroke are the first- and third-leading causes of death in the US, respectively. They also place a staggering financial burden on the US healthcare system, totaling over $259 billion in direct and indirect costs (JNC-VI, 1997).

The incidence of morbidity and mortality from cardiovascular disease increases with age. The average annual rate of first major cardiovascular events increases nearly tenfold from 7 per 1000 at ages 35 to 44 years to 68 per 1000 at ages 85 to 94 years in men, with similar rates observed in women 10 years later in life. One quarter of nursing home residents aged 65 years and older have a primary diagnosis of cardiovascular disease at admission. Furthermore, over 80% of the nearly 950,000 annual deaths from cardiovascular disease occur in people aged 65 years old or older.

The overall estimated prevalence of hypertension was 72 million in 2004 (AHA, Heart Disease and Stroke Statistics, 2007). The relationship between BP and risk of CVD events is continuous, consistent, and independent of other risk factors. The higher the BP, the greater is the chance of heart attack, heart failure, stroke, and kidney disease. For individuals 40–70 years of age, each increment of 20 mmHg in systolic BP (SBP) or 10 mmHg in diastolic BP (DBP) doubles the risk of CVD across the entire BP range from 115/75 to 185/115 mmHg (JNC-7, 2003).

The vast majority of patients with hypertension (93% to 95%) display no demonstrable, curable abnormality of anatomy or physiology (Rudd, 1996). Termed *primary hypertension*, the condition carries no consistent hallmark symptoms or signs, except for the elevated BP itself. Most cases are detected incidentally as part of routine examinations and generally in the absence of target organ damage at initial presentation. Reports of headache, dizziness, fatigue, palpitations, and chest discomfort occur commonly among both patients with hypertension and patients without hypertension. Because the symptoms prompt clinician attention, hypertension is more likely to be detected among patients with symptoms. For the majority of patients with hypertension, symptoms and symptom levels do not correlate well with BP level (Pickering, 2000).

In clinical trials, antihypertensive therapy has been associated with reductions in stroke incidence averaging 35–40%; myocardial infarction, 20–25%; and more than 50% for heart failure. It is estimated that in patients with stage 1 hypertension (SBP 140–159 mmHg and/or DBP 90–99 mmHg) and additional cardiovascular risk factors, achieving a sustained 12 mmHg reduction in SBP over 10 years will prevent 1 death for every 11 patients treated. In the presence of CVD or target organ damage, only 9 patients would require such BP reduction to prevent a death (JNC-7, 2003).

b. The Role of Calcium and the Renin-Angiotensin System (RAS) in Hypertension

Blood pressure is determined by the balance between cardiac output and peripheral resistance, where elevated peripheral resistance is the primary cause of human hypertension. Peripheral resistance is believed to be caused by prolonged smooth muscle contraction of small arterioles as a result of increased intracellular calcium (Beevers 2001). Normally, cells maintain a low resting intracellular concentration of ionized calcium in the face of a large and inwardly directed concentration gradient. As calcium enters the cell, it combines with calcium-binding proteins to stimulate a number of secondary messenger systems and cellular responses, such as nerve excitation, cardiac and vascular smooth muscle contraction, and hormone secretion. Calcium channels can be differentiated into several subtypes, but the L-type channel is the channel that is most directly associated with control of blood pressure. L-type calcium channels are responsible for normal myocardial and smooth vascular muscle contraction (Stern 1992). Prolonged

activation of the L-type calcium channel results in an increased intracellular calcium concentration and subsequent smooth muscle contraction (Stern 1992). Irreversible increases in peripheral resistance have been reported with prolonged smooth muscle constriction and are most likely associated with structural alterations of arteriolar vessels, including thickening of vessel walls (Beevers 2001).

The renin-angiotensin system (RAS), which plays a pivotal role both in the control of blood pressure and the pathogenesis of hypertension, is a complex cascade initiated by the conversion of angiotensinogen into angiotensin I by renin which is a selective enzyme, in the liver (Dina, 2000; Burnier, 2000). Locally, angiotensin I is then converted into angiotensin II, a peptide hormone, primarily in a reaction catalyzed by angiotensin-converting enzyme (ACE; Dina, 2000).

It has been recognized since the 1970's that elevated levels of angiotensin II adversely affect the heart and kidney, and that elevated plasma renin levels increase the risk of myocardial infarction and stroke (Dina, 2000, Burnier, 2000, Burnier, 2001; Yusuf, 2000). Specifically, angiotensin II causes vasoconstriction, proximal tubular sodium reabsorption, inotropism, chronotropism, and alpha-adrenergic receptor stimulation (Dina, 2000). In early animal studies, intravenous administration of angiotensin II was shown to result in renal failure and tubular necrosis (Gavras, 1971). Likewise, early studies in humans found that patients with elevated plasma renin levels had an 11% frequency of heart attacks and a 14% frequency of strokes compared to 0% over the same time period in patients with low serum renin levels (Brunner, 1972).

Research into intervention with the RAS has led to important developments in antihypertensive therapy. Captopril®, introduced in 1981, was the first oral ACE inhibitor (Burnier, 2000). ACE inhibitors, which block the production of angiotensin II, remain an important therapeutic option for patients with hypertension (Burnier, 2000, 2001).

Numerous clinical studies have demonstrated the efficacy of various ACE inhibitors in patients with hypertension, cardiovascular disorders, and renal disorders (Dina, 2000, Burnier, 2001; Yusuf, 2000; CONSENSUS, 1987; SOLVD Investigators, 1991, 1992; Lewis, 1993; Heart Outcomes Prevention Evaluation Study Investigators, 2000). For example, in 1987, the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) concluded that ACE inhibition reduced cardiovascular mortality by 31% after one year and improved symptoms in 127 patients with severe congestive heart failure (CONSENSUS, 1987). In 1991, the Studies of Left Ventricular Dysfunction (SOLVD) reported similar findings (SOLVD Investigators, 1991). The addition of an ACE inhibitor to conventional therapy in patients with reduced left ventricular ejection fractions and congestive heart failure resulted in a 16% reduction in the risk of death compared with placebo. These investigators also found a significant reduction in the rate of heart failure in asymptomatic patients with reduced left ventricular ejection fractions when treated with an ACE inhibitor (SOLVD Investigators, 1992).

In the 1990s, researchers discovered that ACE inhibition also provides significant protection against deterioration of renal function in patients with type 1 diabetes, independent of blood pressure control. ACE-inhibitor therapy was associated with a 50% reduction in the combined endpoints of death, dialysis, and transplantation (Lewis, 1993).

More recently, findings of the Heart Outcomes Prevention Evaluation (HOPE) study led researchers to speculate that the clinical benefit of anti-RAS agents may go beyond reducing blood pressure. The HOPE study demonstrated a significant reduction in the rates of death, myocardial infarction, stroke, other cardiovascular events, and the need for revascularization procedures in high-risk patients following treatment with an ACE inhibitor (ramipril). These benefits, including a 25% reduction in cardiovascular-related mortality, were achieved with only a 2 to 3 mm Hg reduction in blood pressure in patients who were normotensive (139/79 mm Hg) at the time of entry into the study (Yusuf, 2000).

1.2.2 APPROACHES TO TREATMENT

The National High Blood Pressure Education Program (NHBPEP), a division of the National Institutes of Health (NIH), issues national recommendations every four years on the prevention, detection, evaluation, and treatment of high blood pressure. The latest version, JNC-7, was published in JAMA in May 2003 by the NIH with important new changes.

Some of the more important revisions from the previous version are:

- A new category designated prehypertension (combined high normal and normal BP from JNC-VI)
- Stages 2 and 3 hypertension from JNC-VI have been combined (now stage 2 in JNC-7)

- The risk groups based on risk factors and target organ damage have been eliminated
- Thiazide diuretics are recommended initially alone or in combination with an ACE inhibitor, angiotensin receptor blocker, beta blocker, or calcium channel blocker
- The antihypertensive goal for patients with diabetes has been reduced form 130/85 mm Hg to 130/80 mmHg (it is now the same as the ADA Guidelines)
- The risk of CVD begins at a BP of 115/75 mm Hg (even lower than the JNC VI optimal BP of 120/80 mm Hg)
- Most patients will need two or more antihypertensive medications to achieve their BP goal

Americans who are at high risk of cardiovascular disease and associated morbidity and mortality are often not identified, and as a result, do not receive sufficient treatment. A recent report from the National Health and Nutrition Examination Survey (NHANES) conducted in 1999-2000 concluded that 70% were aware of their hypertension, 59% were treated, and 34% had their hypertension controlled. When clinicians fail to prescribe lifestyle modifications, adequate antihypertensive drug doses, or appropriate drug combinations, inadequate BP control may result.

a. JNC-7 Treatment Guidelines

The JNC-7 treatment guidelines classify patients based on blood pressure levels only (Table 8). The 1997 JNC-VI guidelines included risk factor groups in the treatment guidelines. Since then, the new JNC 7 treatment guidelines have been simplified. The new JNC-7 guidelines eliminated the risk factor groups, condensed the 2nd and 3rd stages of hypertension into one stage, and also added a normal classification for hypertension. The NIH recognized that more stringent BP control is required to achieve optimal benefit in high-risk conditions. Treatment of hypertension to these lower levels may provide benefits in preventing stroke, preserving renal function, and slowing the progression of heart failure.

The prehypertension classification (classified as SBP 120-139 mm Hg or DBP 80-89 mm Hg) introduced in JNC 7 is based on the recognition that the virtually linear increase in cardiovascular event risk with increasing blood pressure begins at levels lower than previously recognized (Table 8). It is estimated that about 22% (approximately 46 million) of the adult population falls into the prehypertension category. The intent of the NIH in creating this new designation was to stress lifestyle modification to patients and the need for increased education of healthcare professionals and the public to reduce blood pressure levels and prevent development of hypertension in the general population.

Goal: Treatment goals in JNC-7 remain unchanged from JNC-VI for patients with uncomplicated hypertension in that the NIH recommends that blood pressure should be controlled to below 140/90 mm Hg. In patients who have co-morbidities such as diabetes or chronic kidney disease, the NIH now recommends that BP be controlled to < 130/80 mm Hg (< 130/85 mm Hg in the JNC-VI guidelines).

Treatment: All patients with hypertension should begin with lifestyle modifications. In addition, those patients classified as having prehypertension with a compelling indication, may be managed with lifestyle modifications and drug therapy as well. However, it has always been recognized that once blood pressure rises above the widely recognized threshold of 140/90 mm Hg, it will be necessary to introduce a program of medical treatment. JNC-7 has recognized the *ARB class* for their positive results in recent outcome trials. With the introduction of the ARBs in 1995, JNC VI had not considered this class for any indications due to lack of evidence. However, JNC-7 has recommended ARBs for the following compelling indications: *heart failure, diabetes and chronic kidney disease.* JNC-7 recommends starting with a thiazide diuretic either alone or in combination with one of the other classes of antihypertensives (ACEIs, ARBs, BBs, CCBs) unless there are compelling indications to use other agents. It is recommended that practitioners begin with a low dose of the drug and titrate upward if necessary. Most patients who are hypertensive will require two or more antihypertensive medications to achieve their BP goals. Addition of a second drug from a different class should be initiated when use of a single drug in adequate doses fails to achieve the BP goal. When BP is more than 20/10 mmHg above goal, consideration should be given to initiating therapy with two drugs, either as separate prescriptions or in fixed-dose combinations. The initiation of drug therapy with more than 1 agent may increase the likelihood of achieving the BP goal in a more timely fashion, but particular caution is advised in those at risk for orthostatic hypotension, such as patients with diabetes, autonomic dysfunction, and some older persons. It should be noted that AZOR™ (amlodipine besylate/olmesartan medoxomil) is indicated for the treatment of hypertension, alone or with other antihypertensive agents. This fixed combination drug is not indicated for the initial therapy of hypertension

Table 8: JNC-7 Treatment Guidelines: Classification and Management of Blood Pressure for Adults Aged 18 Years or Older

BP Classification (SBP/DBP mm Hg)	Lifestyle Modification	Initial Drug Therapy Without Compelling Indication	Initial Drug Therapy With Compelling Indications
Normal (< 120 and <80)	Encourage		
Prehypertension (120-139 or 80-89)	Yes	No antihypertensive drug indicated	Drug(s) for the compelling indications*
Stage 1 Hypertension (140-159 or 90-99)	Yes	Thiazide-type diuretics for most; may consider ACEI, ARB, BB, CCB or combination	Drug(s) for compelling indications. Other antihypertensive drugs (diuretics, ACEI, ARB, BB, CCB) as needed
Stage 2 Hypertension (≥160 or ≥100)	Yes	Two-drug combo for most (usually thiazide-type diuretic and ACEI or ARB or BB or CCB)**	

ACEI: angiotensin converting enzyme inhibitor ARB: angiotensin receptor blocker
BB: beta-blocker CCB: calcium channel blocker
*Treat patients with chronic kidney disease or diabetes to BP goal of less than 130/80 mm Hg
** Initial combined therapy should be used cautiously in those at risk for orthostatic hypotension

b. Angiotensin Receptor Blockers (ARBs) in Antihypertensive Therapy

Angiotensin I is converted to angiotensin II via at least two pathways. Best known is the ACE-dependent metabolic pathway, which is generally considered the primary source of systemic angiotensin II. This is the pathway that is blocked by ACE inhibitors. Among the most actively studied alternative metabolic pathways is that mediated by chymase, which is derived from mast cells (Arakawa, 1980). Evidence suggests that chymase-dependent angiotensin II production may be important for some forms of cardiovascular pathology (Uehara, 2000; Warnholtz, 1999; Ihara, 1999).

Regardless of the metabolic pathway involved, angiotensin II activity is mediated by two classes of receptors, known as AT_1 and AT_2. Stimulation of AT_1 receptors is responsible for all the known clinical and cardiovascular pathological effects of angiotensin II. Selective blockade of angiotensin II at AT_1 receptors by angiotensin II receptor blockers results in the antihypertensive and other pharmacologic effects of these drugs. The role of AT_2 receptors is less well understood, although stimulation of these receptors may help counterbalance some of the effects of angiotensin II mediated by AT_1 receptors (Burnier, 2000).

AT_1 receptor blockade has advantages over ACE inhibition, since ARBs block the effects of angiotensin II produced by both ACE-dependent and non-ACE-dependent pathways. In addition, ACE inhibitors block the breakdown of plasma bradykinin, which is thought to result in cough and angioedema, the most common side effects of these drugs (Burnier, 2000). These effects do not occur as a result of AT_1 receptor blockade and may explain why ARBs provide an equally therapeutic and better-tolerated alternative to ACE inhibitors for many patients with hypertension.

c. Calcium Channel Blockers (CCBs) in Antihypertensive Therapy

Calcium channel blockers (or calcium antagonists) represent an important group of agents for the treatment of hypertension. Calcium antagonists exhibit an antihypertensive effect by relaxing vascular smooth muscle through the inhibition of the influx of calcium through the cell membrane via the L-type calcium channels (Elliott 2001). Inhibition of the influx of calcium decreases contraction in myocardial tissue and arteriolar vascular smooth muscle. The vasodilatory properties of calcium channel blockers work to enhance total coronary blood flow due to their ability to decrease vascular tone and resistance in the coronary circulation (Faulkner 2001), thus decreasing total peripheral resistance without significantly affecting cardiac preload.

Depending on the agent and its subtype (non-dihydropyridine or dihydropyridine), calcium antagonists differ in vascular selectivity and other cardio-vascular parameters, particularly in regards to conduction and contractility. Certain agents act more on the calcium of cardiac channels than on the vascular ones and thus have a pronounced negative effect on atrioventricular conduction and contractility (phenylalkylamines), others act more on the channels of the myocytes membranes of the resistance vessels and are thus more vasculo-selective (dihydropyridines), and some act proportionately at the level of the heart and of the arterioles (benzothiazepines). Those derived from the phenylalkylamine and benzothiazepine (or non-dihydropyridine) subtype decrease the conductivity, excitability and the contractility of the heart (Hernandez-Hernandez, 2002).

A marked decrease in arterial blood pressure and dilation of resistance vessels elicits the activation of sympathetic reflexes that may result in reflex tachycardia. Reflex tachycardia is particularly evident in the short-acting agents with rapid absorption (1st generation dihydropyridines). The newer 2nd generation agents, including amlodipine, have characteristically slower starting effects and a longer duration of action, thus making them favorable for the use in long-term antihypertensive treatment with a decreased incidence of reflex tachycardia as compared to their shorter-acting predecessors (Hernandez-Hernandez, 2002). Additionally, because amlodipine's affinity for vascular tissue is much greater than its affinity for the myocardium, lower doses may be used to maintain its antihypertensive effect without reducing the contractility of myocardial tissue; a factor that is beneficial for patients whom negative inotropy might be an issue (Faulkner 2001). Thus, calcium antagonists have shown to play an integral role in the chronic treatment of hypertension, proving efficacious when used as monotherapy as well as in combination.

d. Place of Combination Products in Hypertension Therapy

Guidelines relating to the treatment of hypertension are consistently updated with new blood pressure goal ranges. Goal ranges have been on the decline for decades, making it increasingly more difficult for physicians to adequately treat patients to goal with single agent therapy (Stergiou 2006). Current evidence suggests that the majority of patients treated for hypertension, roughly two thirds of the diagnosed population, will require combination therapy in order to achieve targeted blood pressure goals (Sica 2002, Stergiou 2006, Tejada 2007). Combination therapy is required when a patient is unable to reach goal with the use of a single agent in combination with diet and exercise modifications. Therapy utilizing multiple anti-hypertensive agents, from diverse yet complimentary classes, provides a mechanism to target the disease through multiple physiologic actions (Faulkner 2001, Sica 2002). It is estimated that a therapeutic success rate of 80-90% is achieved with the use of multiple antihypertensive agents as compared to single-agent therapy. The ALLHAT study reported similar estimates, disclosing that 63% of study patients required combination therapy of two or more drugs to reach blood pressure goals (Stergiou 2006). JNC-7 states that combination therapy utilizing two or more agents is generally required to maintain adequate blood pressure control. JNC-7 guidelines recommend initiation of two drugs in patients presenting with systolic blood pressure >20 mmHg above goal or diastolic blood pressure >10 mmHg above goal. This recommendation is made based upon evidence showing that combination therapy increases the probability of achieving blood pressure goals within a shorter time period as compared to initiating single drug therapy (Chobanian 2004).

Combination therapy has been reported to increase clinical efficacy, offset adverse events observed with monotherapy, and increase compliance (Tejada 2007). Monotherapy often results in the stimulation of compensatory mechanisms, thus diminishing overall efficacy (Faulkner 2001). By combining multiple agents, regulatory mechanisms potentiated by one drug may be counter-balanced by the activity of another drug (Sica 2002). Additionally, single agent therapy regularly requires use of the maximum daily dose, resulting in an increased incidence of adverse events. The increased risk of side effects has been associated with decreased compliance rates and subsequent therapeutic failure (Faulkner 2001). A study comparing the use of a fixed combination of ramapril/felodipine with the component monotherapies, reported a significantly greater responder rate, 71.4% for the combination and 41.2% and 28.6% for the respective monotherapies. This finding was attributed to reduced adverse event prevalence in patients receiving the combination agent (Scholze 2006). A separate study looking at adherence patterns, evaluated patients receiving a fixed dose combination (FDC) of amlodipine and benazepril compared to patients taking an ACE inhibitor and a dihydropyridine calcium channel blocker as separate agents, and found adherence rates of 87.9% and 69.2%, respectively. Greater adherence to the fixed dose combination was due to regimen simplification (Gerbino 2007). Studies have also shown that FDCs, like standard combination therapies, are generally better tolerated as lower doses of the component monotherapies are required, and improved blood pressure lowering over component monotherapy has been reported (Tejada 2007).

1.3 EVIDENCE FOR PHARMACOGENOMIC TESTS AND DRUGS

Not applicable.

2. SUPPORTING CLINICAL AND ECONOMIC INFORMATION

2.1 SUMMARIZING KEY CLINICAL AND ECONOMIC STUDIES

A Randomized, Double-Blind, Placebo-Controlled Factorial Study Evaluating The Efficacy and Safety of Co-Administration of Amlodipine Besylate Plus Olmesartan Medoxomil Compared to Monotherapy in Patients with Mild to Severe Hypertension (Blinded-Study Phase, Phase III, United States)

Objectives: The main objective of the blinded-phase (day 1 to week 8) of this pivotal trial was to determine if co-administration of amlodipine besylate (AML) and olmesartan medoxomil (OM) would have a clinically significant benefit versus the respective monotherapy components in controlling blood pressure in patients with mild to severe hypertension.

The primary efficacy endpoint was the change from baseline in SeDBP at the end of Period II (Week 8). If a patient withdrew from the study prior to Week 8, the last observed value during the randomized, double-blind treatment period was carried forward (LOCF) for the primary efficacy analysis. Change from baseline in SeSBP at the end of Period II with LOCF was the secondary efficacy variable.

Secondary endpoints also included the number (percentage) of patients achieving blood pressure goal (defined as blood pressure <140/90 mm Hg, <130/80 mm Hg for patients with diabetes). In addition, change from baseline in SeDBP and SeSBP at weeks 2, 4, 6, and 8 without LOCF were evaluated.

Methodology:

The 8-week, multi-center, randomized, double-blind, placebo-controlled, parallel-group factorial study was designed to assess the efficacy and safety of co-administration of amlodipine (AML) plus olmesartan medoxomil (OM) in adult patients (N=1940 patients; 384 patients ≥65 years of age) with mild to severe hypertension, in comparison to the respective monotherapies. This 8-week study was a part of a 52-week trial which consisted of 3 periods: 1) a washout period of approximately 2 weeks, 2) an 8-week, double-blind treatment period, and 3) a 44-week, open-label treatment period. Period I of this study consisted of a single screening visit for patients not on antihypertensive medications and a two-week washout period for patients on antihypertensive medications. To be eligible for randomization, all patients (males and females ≥18 years of age) had to have a mean SeDBP ≥95 mm Hg and ≤120 mmHg, with ≤10 mmHg difference between the pre-randomization and the randomization visit BP measurements.

Period II (double-blind) consisted of an 8-week treatment period. Patients who met all of the inclusion criteria and none of the exclusion criteria were randomized equally to one of the following 12 treatment arms: placebo, monotherapy treatment with amlodipine 5 mg or 10 mg, monotherapy treatment with olmesartan medoxomil 10 mg, 20 mg, or 40 mg, or combination therapy with amlodipine/olmesartan medoxomil at doses of 5/10 mg, 5/20 mg, 5/40 mg, 10/10 mg, 10/20 mg, and 10/40 mg. Patients were discontinued from the study if SeSBP was <90 mm Hg or SeDBP was >120 mmHg at any visit during Period II. The ITT (Intent-to-Treat) population was the primary analysis population for efficacy evaluations. The ITT population included patients who took at least 1 dose of randomized double-blind study medication, had baseline blood pressure measurements, and at least 1 blood pressure measurement after taking randomized double-blind study medication.

Treatment was double-blind, parallel-arm for all randomized patients. To achieve even distribution among treatment groups within each stratum, the randomization process included stratification factors for age group (≥65 years, <65 years) and diabetic status. This study targeted approximately 20% of the patients to be ≥ 65 years of age.

Period III consisted of a 44-week, open-label treatment period to assess long-term safety and efficacy of combination therapy with amlodipine 5 mg plus olmesartan medoxomil 40 mg. During the open-label extension, patients whose blood pressure was not adequately controlled (i.e., did not achieve a blood pressure goal of <140/90 mm Hg, or <130/80 mmHg for those patients with diabetes) on amlodipine 5 mg plus olmesartan medoxomil 40 mg were titrated to amlodipine 10 mg plus olmesartan 40 mg. Patients whose blood pressure was still not adequately controlled were offered hydrochlorothiazide 12.5 mg and subsequently 25 mg as required to achieve adequate blood pressure goal. Patients were discontinued from the study if SeDBP was >120 mm Hg at any visit during Period III while on maximal

therapy. If a patient experienced symptoms of hypotension or displayed intolerance to study medication at any time during Period III, the patient was back-titrated at the investigator's discretion. After Week 52, patients were discontinued from the study and treated per investigator's discretion. A follow-up visit two weeks later (Week 54) was scheduled to examine any safety issues.

Safety assessments included adverse events, evaluation of edema, clinical laboratory measurements of hematology and biochemistry, vital signs, physical examinations and 12-lead ECG assessments.

In the double-blind period, subgroup analyses were performed for each of the following groups: age group (<65 years, ≥65 years), diabetic status (yes, no), gender (male, female), race (Black, non-Black), ethnicity (Hispanic/Latino, non-Hispanic/Latino), hypertension class (Stage 1 hypertension, Stage 2 hypertension), prior antihypertensive medication use (naïve to antihypertensive medication, not naïve to antihypertensive medication), and baseline BMI (>30 kg/m^2, ≤30 kg/m^2).

Results (**Period II, Double-Blind):**

Overall Baseline Characteristics: Of the 4,234 patients screened for the study, 1,940 subjects were randomized equally into the 12 treatment arms for the double blind phase of the study. Of those randomized, 251 subjects were discontinued and 1,923 subjects were considered part of the intent to treat (ITT) population. Of the ITT population, 1,689 subjects completed the study.

Baseline characteristics for this study appear in Table 9, below. The treatment groups were comparable with respect to demographics, with no statistically significant differences among the treatment groups. Weight, height, and Body Mass Index (BMI) were also similar for the treatment groups, with no statistically significant differences among the treatment groups for these baseline characteristics. Treatment groups were also similar with respect to baseline values for blood pressure and heart rate, with no statistically significant differences among the treatment groups.

In regards to baseline hypertension class for the Safety Population, the treatment groups were similar, with over 70% of patients in each treatment group having Stage 2 hypertension. Overall, a total of 1538 (79.3%) patients had Stage 2 hypertension.

Table 9: Baseline characteristics of randomized subjects (N =1,940)

Age (years, mean ± SD)	54.0 ± 11.1
≥ 65 y (%)	19.8
≥ 75 y (n, %)	3.2
Males (%)	54.3
Blacks (%)	24.8
Subjects with diabetes (%)	13.5
Subjects anti-hypertensive agent naïve (%)	34.3
BMI (kg/$M^{2,}$ mean ± SD)	33.5 ± 7.1
SBP (mm Hg, mean ± SD)	163.8 ± 16.1
DBP (mm Hg, mean ± SD)	101.6 ± 5.2
Weight (kg, mean ± SD)	95.1 ± 21.9
Height (cm, mean ± SD)	170.1 ± 10.4
BMI (kg/m^2, mean ± SD)	33.5 ± 7.1
Patients with BMI ≥ 30 kg/m^2 (%)	64.7
SD = standard deviation, BMI = body mass index, SBP = systolic blood pressure, DBP = diastolic blood pressure	

Efficacy Results: Each combination therapy had significantly greater reductions in SeDBP and SeSBP compared to both of its monotherapy components (Table 10, below).

Table 10: Mean Change in SeDBP and SeSBP (mm Hg) from Baseline to Week 8 with LOCF – Combination Therapy versus Monotherapy Comparisons – Intent to Treat Population

Treatment Comparison			SeDBP Difference (Tmt 1 – Tmt 2)		SeSBP Difference (Tmt 1 – Tmt 2)	
Tmt 1	**vs.**	**Tmt 2**	**LS Mean (SE)**	**p-value**	**LS Mean (SE)**	**p-value**
AML5/OM10	vs.	OM10	-5.5 (0.99)	<0.0001	-11.7 (1.64)	<0.0001
	vs.	AML5	-4.3 (0.99)	<0.0001	-8.2 (1.63)	<0.0001
AML5/OM20	vs.	OM20	-4.7 (1.00)	<0.0001	-9.9 (1.65)	<0.0001
	vs.	AML5	-4.6 (0.99)	<0.0001	-8.3 (1.64)	<0.0001
AML5/OM40	vs.	OM40	-5.4 (1.00)	<0.0001	-9.7 (1.65)	<0.0001
	vs.	AML5	-6.3 (1.00)	<0.0001	-10.8 (1.65)	<0.0001
AML10/OM10	vs.	OM10	-7.8 (0.99)	<0.0001	-13.9 (1.64)	<0.0001
	vs.	AML10	-3.3 (0.99)	0.0004	-5.9 (1.63)	0.0002
AML10/OM20	vs.	OM20	-7.8 (1.00)	<0.0001	-15.4 (1.65)	<0.0001
	vs.	AML10	-4.4 (0.99)	<0.0001	-9.2 (1.64)	<0.0001
AML10/OM40	vs.	OM40	-8.5 (0.99)	<0.0001	-13.0 (1.64)	<0.0001
	vs.	AML10	-6.1 (0.99)	<0.0001	-9.6 (1.63)	<0.0001

LS Mean, SE, 95% CI, and one-sided p-values were obtained from an Analysis of Covariance model with fixed effects for treatment, age group, and diabetic status, and baseline as a covariate.
AML = amlodipine, OM = olmesartan medoxomil, LS = least squares, SE = standard error, SeDBP = seated diastolic blood pressure, SeSBP = seated systolic blood pressure, Tmt = treatment.

The table (11) below presents the analysis results for mean change in SeDBP and SeSBP from baseline to Week 8 with LOCF for the ITT population. Each active treatment group had a statistically significant mean reduction in SeDBP and SeSBP from baseline to Week 8 with LOCF (p<0.0001). Mean reductions in SeDBP and SeSBP were greater in the combination therapy groups compared with the monotherapy groups. In the combination groups with AML 5 mg and 10 mg, increasing doses of OM (10 mg, 20 mg, and 40 mg) resulted in greater reductions in SeDBP. Overall, the greatest reductions in seated blood pressure occurred in the group treated with AML 10 mg + OM 40 mg (-30.1/-19.0 mm Hg) followed by the group treated with AML 10 mg + OM 20 mg (-29.2/-17.0 mmHg).

Table 11: Mean Change in SeDBP and SeSBP (mm Hg) from Baseline to Week 8 with LOCF – Intent to Treat Population

		SeDBP Baseline to Week 8 with LOCF		SeSBP Baseline to Week 8 with LOCF	
Treatment	**N[1]**	**Change Mean ± SD**	**p-value[2]**	**Change Mean ± SD**	**p-value[2]**
Placebo	160	-3.1 ± 10.67	<0.0001	-4.8 ± 18.70	0.0235
OM10	160	-8.3 ± 9.28	<0.0001	-11.5 ± 15.23	<0.0001
OM20	159	-9.2 ± 9.73	<0.0001	-13.8 ± 15.90	<0.0001
OM40	160	-10.2 ± 10.69	<0.0001	-16.1 ± 16.58	<0.0001
AML5	161	-9.4 ± 8.25	<0.0001	-14.9 ± 14.95	<0.0001
AML10	163	-12.7 ± 8.25	<0.0001	-19.7 ± 16.52	<0.0001
AML5/OM10	163	-13.8 ± 7.48	<0.0001	-24.2 ± 13.96	<0.0001
AML5/OM20	160	-14.0 ± 9.07	<0.0001	-23.6 ± 14.86	<0.0001
AML5/OM40	157	-15.5 ± 8.15	<0.0001	-25.4 ± 14.70	<0.0001
AML10/OM10	161	-16.0 ± 8.62	<0.0001	-25.3 ± 14.88	<0.0001
AML10/OM20	158	-17.0 ± 8.04	<0.0001	-29.2 ± 16.72	<0.0001
AML10/OM40	161	-19.0 ± 8.90	<0.0001	-30.1 ± 15.91	<0.0001

[1]N was the number of patients with values at both time points.
[2]P-values were obtained from an Analysis of Covariance model with fixed effects for treatment, age group, and diabetic status, and baseline as a covariate.
Week 8 with LOCF was defined as the last available measurement during the double-blind, active treatment period.
AML = amlodipine, OM = olmesartan medoxomil, SD = standard deviation, SeDBP = seated diastolic blood pressure, SeSBP = seated systolic blood pressure

Analysis results for the mean change in SeDBP and SeSBP from baseline to Week 2, Week 4, Week 6 and Week 8 without LOCF for the ITT population were similar to the results observed at Week 8 with LOCF. For all active treatment groups, most of the mean reduction in the SeDBP and SeSBP occurred from baseline to Week 2, and plateaued by Week 4.

The greater blood pressure reductions achieved with the combination treatments, compared with the respective monotherapies, resulted in a comparatively greater percentage of patients on combination therapy achieving their blood pressure treatment goals. The percentage of patients achieving their blood pressure goals by Week 8 with LOCF ranged from 20.0% to 36.3% for the groups treated with monotherapy compared with 35.0% to 53.2% for the groups treated with combination therapy. Approximately 50% of patients treated with one of the higher dose combination therapies (i.e., AML 10mg + OM 10 mg, AML 10 mg + OM 20 mg, AML 5 mg + OM 40 mg, and AML 10 mg + OM 40 mg) reached their blood pressure goal by Week 8 with LOCF.

In addition, the percentage of patients brought to a goal blood pressure of <140/90 mmHg ranged from 22.5% to 38.1% among the 5 monotherapy groups compared to 38.7% to 56.3% among the 6 combination therapy groups.

Safety: A total of 1020 (52.6% of 1940) patients experienced a treatment-emergent adverse event (TEAE) during the study. Across the 12 treatment groups the percentage experiencing a TEAE ranged from 45.3% to 58.9%, with no apparent trend in the distribution of TEAEs among the treatment groups (placebo incidence: 56.2%). Drug-related TEAEs were experienced by a total of 521 (26.9%) patients, ranging from 19.6% to 33.1% with the incidence in the placebo group being 29.6%. Across all treatment groups, most TEAEs and drug-related TEAEs were considered mild in intensity.

A total of 114 (5.9%) patients were discontinued from the study due to an adverse event. Edema was the most common drug-related TEAE and was experienced by a total of 277 (14.3%) patients. Edema was proactively assessed, and as a result, the observed incidences were higher than that reported in the package inserts for the components. There was a greater frequency of treatment-emergent edema among the groups that used AML 10 mg as a component of their treatment, with the AML 10 mg monotherapy group (36.8%) having the greatest incidence of edema. There appeared to be a decrease in the incidence when AML 10 mg was combined with OM 10 mg, 20 mg, and 40 mg (26.5%, 25.6%, and 23.5%). This reduction in the incidence of edema was not seen when AML 5mg was combined with OM 10 mg, 20 mg, or 40 mg (20.9%, 18.0%, and 18.5%) compared to AML 5 mg monotherapy group (13.0%). Other more common drug-related TEAEs included headache, experienced by 66 (3.4%) patients and dizziness experienced by 50 (2.6%) patients.

The frequency of hypertension (including the preferred terms of hypertension, systolic hypertension, diastolic hypertension, accelerated hypertension, blood pressure increased, blood pressure diastolic increased, or blood pressure inadequately controlled) reported as an adverse event was greatest in the placebo group (8.0%) and ranged from 0.6% to 5.0% among the active treatment groups. The combination treatment groups had a 0.0% to 1.9% incidence of adverse event of hypertension (lack of efficacy) reported as an adverse event.

A total of 7 patients experienced drug-related hypotension (1 patient in the OM 10 mg group, 2 patients in the OM 10 mg + AML 10 mg group, 1 patient in the OM 20 mg + AML 10 mg group, 1 patient in the OM 40 mg + AML 5 mg group, and 2 patients in the OM 40 mg + AML 10 mg treatment group).

There were no laboratory measurements that signified a safety concern. Furthermore, there were no clinically meaningful changes in heart rates, ECGs, or physical examinations for any treatment group during the study.

A Randomized, Double-Blind, Placebo-Controlled Factorial Study Evaluating The Efficacy and Safety of Co-Administration of Amlodipine Besylate Plus Olmesartan Medoxomil Compared to Monotherapy in Patients with Mild to Severe Hypertension (Subgroup Analyses of Blinded-Study Phase, United States)

Subgroup Analyses: Analyses of prospectively identified subgroups from the 8-week controlled phase of this study. Subgroups were analyzed by age (<65 years vs. ≥65 years), diabetic status (subjects without diabetes vs. those with), and by race (Blacks vs. non-Blacks).

Analysis by Age

The mean baseline SeDBP for each subgroup was 102.0 mm Hg for subjects <65 years of age and 100.3 mm Hg for the subgroup ≥65 years of age. For both age subgroups, each active treatment group had a statistically significant mean reduction in SeDBP from baseline to Week 8 with LOCF ($p<0.0001$). The result of this subgroup analysis appears in Table 12, below.

Table 12: Mean change in SeDBP (mm Hg) from Baseline to Week 8 with LOCF Stratified by Age Subgroups – Intent to Treat Population

	<65 Years of Age			≥65 Years of Age		
Treatment (mg)	N[1]	Change Mean ± SD	p-value[2]	N[1]	Change Mean ± SD	p-value[2]
Placebo	128	-2.2 ± 10.69	0.0104	32	-6.4 ± 10.06	<0.0001
OM 10	128	-7.8 ± 9.03	<0.0001	32	-10.1 ± 10.13	<0.0001
OM 20	129	-8.3 ± 9.66	<0.0001	30	-13.2 ± 9.15	<0.0001
OM 40	129	-10.6 ± 10.07	<0.0001	31	-8.8 ± 13.04	<0.0001
AML 5	129	-8.3 ± 7.62	<0.0001	32	-13.7 ± 9.37	<0.0001
AML 10	131	-11.9 ± 8.27	<0.0001	32	-16.1 ± 7.33	<0.0001
AML 5/OM 10	131	-13.8 ± 7.84	<0.0001	32	-13.9 ± 5.85	<0.0001
AML 5/OM 20	126	-13.9 ± 8.97	<0.0001	34	-14.6 ± 9.54	<0.0001
AML 5/OM 40	126	-15.5 ± 8.44	<0.0001	31	-15.8 ± 6.96	<0.0001
AML 10/OM 10	130	-15.8 ± 8.59	<0.0001	31	-16.8 ± 8.83	<0.0001
AML 10/OM 20	126	-17.3 ± 8.07	<0.0001	32	-15.9 ± 7.98	<0.0001
AML 10/OM 40	128	-18.5 ± 9.17	<0.0001	33	-20.9 ± 7.59	<0.0001

[1]N was the number of subjects with values at both time points.
[2]Two-sided p-values were obtained from an Analysis of Covariance model with treatment, age subgroup, and treatment-by subgroup interaction as fixed effects and baseline blood pressure as a covariate.
AML = amlodipine, OM = olmesartan medoxomil, SD = standard deviation.

For both age subgroups, subjects treated with AML 10 mg + OM 40 mg demonstrated the greatest overall mean reductions in SeDBP.

With respect to the systolic BP analysis, the mean baseline SeSBP was 161.4 mm Hg for the subgroup <65 years of age and 173.6 mm Hg for the subgroup ≥65 years of age. The results of this analysis appear in Table 13, below.

Table 13: Mean change in SeSBP (mm Hg) from Baseline to Week 8 with LOCF Stratified by Age Subgroups – Intent to Treat Population

	<65 Years of Age			≥65 Years of Age		
Treatment (mg)	N[1]	Change Mean ± SD	p-value[2]	N[1]	Change Mean ± SD	p-value[2]
Placebo	128	-4.1 ± 18.54	0.0015	32	-7.9 ± 19.33	0.3430
OM 10	128	-10.9 ± 15.30	<0.0001	32	-13.9 ± 14.92	0.0002
OM 20	129	-12.5 ± 15.07	<0.0001	30	-19.4 ± 18.29	<0.0001
OM 40	129	-16.2 ± 15.63	<0.0001	31	-15.7 ± 20.33	<0.0001
AML 5	129	-13.3 ± 13.44	<0.0001	32	-21.1 ± 18.94	<0.0001
AML 10	131	-18.8 ± 16.39	<0.0001	32	-23.4 ± 16.82	<0.0001
AML 5/OM 10	131	-23.3 ± 14.38	<0.0001	32	-27.5 ± 11.70	<0.0001
AML 5/OM 20	126	-23.5 ± 15.38	<0.0001	34	-24.0 ± 12.95	<0.0001
AML 5/OM 40	126	-25.1 ± 13.62	<0.0001	31	-26.8 ± 18.66	<0.0001
AML 10/OM 10	130	-25.1 ± 14.79	<0.0001	31	-26.3 ± 15.45	<0.0001
AML 10/OM 20	126	-28.9 ± 15.86	<0.0001	32	-30.4 ± 19.98	<0.0001
AML 10/OM 40	128	-29.1 ± 16.30	<0.0001	33	-33.9 ± 13.88	<0.0001

[1]N was the number of subjects with values at both time points.
[2]Two-sided p-values were obtained from an Analysis of Covariance model with treatment, age subgroup, and treatment-by subgroup interaction as fixed effects and baseline blood pressure as a covariate.
AML = amlodipine, OM = olmesartan medoxomil, SD = standard deviation.

For both age subgroups, each active treatment group demonstrated a statistically significant mean reduction in SeSBP from baseline to Week 8 with LOCF ($p<0.001$). For both age subgroups, the magnitude of the response was similar. The greatest mean reductions in SeSBP occurred in the group of subjects treated with AML 10 mg + OM 40 mg.

With respect to comparisons of combination therapy versus monotherapy for SeDBP and SeSBP (from baseline to Week 8 with LOCF) in patients less than 65 years of age, each combination therapy had a significantly greater mean reduction in SeDBP and SeSBP compared to the respective monotherapy components ($p<0.001$ for all comparisons).

For patients greater than or equal to 65, not all comparisons of combination therapy versus monotherapy resulted in significantly greater reductions for mean change in SeDBP and SeSBP from baseline to Week 8 with LOCF. Table 14 provides results of the comparisons between combination therapy versus monotherapy for patients greater than or equal to 65.

Table 14: Mean Change in SeDBP and SeSBP (mm Hg) from Baseline to Week 8 with LOCF – Combination Therapy Versus Monotherapy Comparisons – Patients ≥ 65 Years of Age

Treatment Comparison			SeDBP Difference (Tmt 1 – Tmt 2)		SeSBP Difference (Tmt 1 – Tmt 2)	
Tmt 1	**vs.**	**Tmt 2**	**LS Mean (SE)**	**p-value**	**LS Mean (SE)**	**p-value**
AML5/OM10	vs.	OM10	-3.9 (2.22)	0.0380	-14.1 (3.68)	<0.0001
	vs.	AML5	-0.2 (2.22)	0.4633	-6.6 (3.68)	0.0367
AML5/OM20	vs.	OM20	-1.3 (2.22)	0.2742	-6.0 (3.69)	0.0523
	vs.	AML5	-0.8 (2.18)	0.3655	-4.2 (3.63)	0.1254
AML5/OM40	vs.	OM40	-7.4 (2.25)	0.0005	-12.9 (3.74)	0.0003
	vs.	AML5	-2.3 (2.23)	0.1467	-7.8 (3.71)	0.0183
AML10/OM10	vs.	OM10	-6.6 (2.23)	0.0017	-14.3 (3.71)	<0.0001
	vs.	AML10	-0.5 (2.23)	0.4174	-3.5 (3.71)	0.1748
AML10/OM20	vs.	OM20	-2.8 (2.25)	0.1057	-12.2 (3.74)	0.0006
	vs.	AML10	0.1 (2.22)	0.4767	-7.0 (3.68)	0.0282
AML10/OM40	vs.	OM40	-11.9 (2.22)	<0.0001	-15.7 (3.69)	<0.0001
	vs.	AML10	-4.5 (2.20)	0.0207	-7.2 (3.66)	0.0250

LS Mean, SE, 95% CI, and one-sided p-values were obtained from an Analysis of Covariance model with fixed effects for treatment, age group, and diabetic status, and baseline as a covariate.
AML = amlodipine, OM = olmesartan medoxomil, LS = least squares, SE = standard error, SeDBP = seated diastolic blood pressure, SeSBP = seated systolic blood pressure, Tmt = treatment.

For the subgroup of patients <65 years of age, approximately 51% to 56% of patients treated with one of the higher dose combination therapies (i.e., AML 10 mg + OM 10 mg, AML 10 mg + OM 20 mg, AML 5 mg + OM 40 mg, and AML 10 mg + OM 40 mg) reached their blood pressure goal.

The subgroup of patients ≥65 years of age had a comparatively lower percentage of patients who reached their blood pressure goal, which was likely due to the higher baseline SeSBP in this subgroup. The mean baseline blood pressure for patients ≥ 65 was 173.6/100.3 mm Hg. Approximately 21% to 44% of patients treated with one of the higher dose combination therapies (i.e., AML 10 mg + OM 10 mg, AML 10 mg + OM 20 mg, AML 5 mg + OM 40 mg, and AML 10 mg + OM 40 mg) reached their blood pressure goal.

Analysis by Diabetes Status

The mean baseline SeDBP was 101.7 mmHg for the subgroup of subjects without diabetes and 101.1 mm Hg for the subgroup of subjects with diabetes. For both subgroups, each active treatment group had a statistically significant mean reduction in SeDBP from baseline to Week 8 with LOCF ($p<0.0001$). The results of this subgroup analysis appear in Table 15, below

Table 15. Mean change in SeDBP (mm Hg) from Baseline to Week 8 with LOCF Stratified by Diabetes Status – Intent to Treat Population

	Without Diabetes			With Diabetes		
Treatment (mg)	N[1]	Change Mean ± SD	p-value[2]	N[1]	Change Mean ± SD	p-value[2]
Placebo	137	-2.2 ± 9.63	0.0065	23	-8.2 ± 14.77	<0.0001
OM 10	140	-8.0 ± 9.50	<0.0001	20	-9.9 ± 7.50	<0.0001
OM 20	137	-9.2 ± 9.38	<0.0001	22	-9.4 ± 11.96	<0.0001
OM 40	139	-10.5 ± 10.33	<0.0001	21	-8.3 ± 12.94	<0.0001
AML 5	139	-9.0 ± 7.86	<0.0001	22	-11.6 ± 10.36	<0.0001
AML 10	140	-12.9 ± 8.35	<0.0001	23	-11.7 ± 7.69	<0.0001
AML 5/OM 10	140	-13.6 ± 7.65	<0.0001	23	-15.1 ± 6.34	<0.0001
AML 5/OM 20	138	-14.9 ± 9.02	<0.0001	22	-8.3 ± 7.23	<0.0001
AML 5/OM 40	140	-15.6 ± 8.16	<0.0001	17	-14.6 ± 8.26	<0.0001
AML 10/OM 10	141	-16.0 ± 8.49	<0.0001	20	-16.0 ± 9.75	<0.0001
AML 10/OM 20	137	-17.3 ± 8.26	<0.0001	21	-15.0 ± 6.20	<0.0001
AML 10/OM 40	137	-19.1 ± 9.08	<0.0001	24	-18.4 ± 7.95	<0.0001

[1]N was the number of subjects with values at both time points.
[2]Two-sided p-values were obtained from an Analysis of Covariance model with treatment, diabetes status subgroup, and treatment-by subgroup interaction as fixed effects and baseline blood pressure as a covariate.
AML = amlodipine, OM = olmesartan medoxomil, SD = standard deviation.

For the subgroup of subjects without diabetes, increases in dose were associated with progressively greater mean reductions in SeDBP across all treatment groups, which was less consistent for the subgroup of subjects with diabetes. These findings may be a consequence of the relatively small number of subjects with diabetes in each treatment group. Overall, the greatest mean reductions in SeDBP occurred in the group of subjects treated with AML 10 mg + OM 40 mg.

The mean baseline SeSBP was 163.1 mmHg for the subgroup of subjects without diabetes and 168.6 mmHg for the subgroup of subjects with diabetes. For both subgroups, each active treatment group showed a statistically significant mean reduction in SeSBP from baseline to Week 8 with LOCF ($p<0.003$). The results of this subgroup analysis appear in Table 16, below.

Table 16. Mean Change in SeSBP (mm Hg) from Baseline to Week 8 with LOCF Stratified by Diabetes Status – Intent to Treat Population

	Without Diabetes			With Diabetes		
Treatment (mg)	N[1]	Change Mean ± SD	p-value[2]	N[1]	Change Mean ± SD	p-value[2]
Placebo	137	-3.1 ± 15.50	0.0368	23	-15.3 ± 30.18	0.0003
OM 10	140	-11.1 ± 15.58	<0.0001	20	-14.4 ± 12.49	<0.0001
OM 20	137	-14.2 ± 15.70	<0.0001	22	-11.6 ± 17.28	0.0010
OM 40	139	-16.9 ± 15.88	<0.0001	21	-10.5 ± 20.17	0.0026
AML 5	139	-14.0 ± 14.29	<0.0001	22	-20.3 ± 18.04	<0.0001
AML 10	140	-20.1 ± 16.72	<0.0001	23	-17.7 ± 15.48	<0.0001
AML 5/OM 10	140	-23.9 ± 13.87	<0.0001	23	-25.6 ± 14.79	<0.0001
AML 5/OM 20	138	-25.1 ± 14.67	<0.0001	22	-14.2 ± 12.67	<0.0001
AML 5/OM 40	140	-25.5 ± 14.23	<0.0001	17	-25.0 ± 18.65	<0.0001
AML 10/OM 10	141	-25.0 ± 14.33	<0.0001	20	-27.9 ± 18.49	<0.0001
AML 10/OM 20	137	-29.7 ± 16.92	<0.0001	21	-26.3 ± 15.44	<0.0001
AML 10/OM 40	137	-30.1 ± 16.40	<0.0001	24	-30.3 ± 13.08	<0.0001

[1]N was the number of subjects with values at both time points.
[2]Two-sided p-values were obtained from an Analysis of Covariance model with treatment, diabetes status subgroup, and treatment-by subgroup interaction as fixed effects and baseline blood pressure as a covariate.
AML = amlodipine, OM = olmesartan medoxomil, SD = standard deviation.

As observed for SeDBP, increases in dose were associated with progressively greater mean reductions in SeSBP for the subgroup of subjects without diabetes across all treatment groups, which was less consistent for the subgroup of subjects with diabetes. Similarly, these findings may be a consequence of the relatively small number of subjects with diabetes in each treatment group. In addition, the greatest mean reductions in SeDBP occurred in the group of subjects treated with AML 10 mg + OM 40 mg.

With respect to comparisons of combination therapy versus monotherapy for SeDBP and SeSBP (from baseline to Week 8 with LOCF) in patients without diabetes, each combination therapy had a significantly greater mean reduction in SeDBP and SeSBP compared to both of its monotherapy components ($p<0.0016$ for all comparisons).

For patients with diabetes, not all comparisons of combination therapy versus monotherapy resulted in significantly greater reductions for mean change in SeDBP and SeSBP from baseline to Week 8 with LOCF. Table 17 provides results of the comparisons between combination therapy versus monotherapy for patients with diabetes.

Table 17: Mean Change in SeDBP and SeSBP (mm Hg) from Baseline to Week 8 with LOCF – Combination Therapy Versus Monotherapy Comparisons – Patients With Diabetes

Treatment Comparison			SeDBP Difference (Tmt 1 – Tmt 2)		SeSBP Difference (Tmt 1 – Tmt 2)	
Tmt 1	**vs.**	**Tmt 2**	**LS Mean (SE)**	**p-value**	**LS Mean (SE)**	**p-value**
AML5/OM10	vs.	OM10	-4.5 (2.72)	0.0494	-7.1 (4.48)	0.0566
	vs.	AML5	-3.5 (2.65)	0.0921	-4.2 (4.37)	0.1655
AML5/OM20	vs.	OM20	1.0 (2.68)	0.3563	-3.7 (4.41)	0.1982
	vs.	AML5	3.2 (2.68)	0.1141	4.1 (4.42)	0.1764
AML5/OM40	vs.	OM40	-6.5 (2.90)	0.0121	-14.8 (4.78)	0.0010
	vs.	AML5	-3.1 (2.87)	0.1375	-6.2 (4.73)	0.0935
AML10/OM10	vs.	OM10	-5.5 (2.82)	0.0265	-10.2 (4.63)	0.0138
	vs.	AML10	-4.4 (2.72)	0.0529	-9.6 (4.48)	0.0162
AML10/OM20	vs.	OM20	-5.9 (2.71)	0.0154	-14.5 (4.47)	0.0006
	vs.	AML10	-3.5 (2.69)	0.0935	-8.9 (4.42)	0.0219
AML10/OM40	vs.	OM40	-10.0 (2.66)	<0.0001	-18.1 (4.38)	<0.0001
	vs.	AML10	-6.5 (2.60)	0.0061	-11.8 (4.27)	0.0030

LS Mean, SE, 95% CI, and one-sided p-values were obtained from an Analysis of Covariance model with fixed effects for treatment, age group, and diabetic status, and baseline as a covariate.
AML = amlodipine, OM = olmesartan medoxomil, LS = least squares, SE = standard error, SeDBP = seated diastolic blood pressure, SeSBP = seated systolic blood pressure, Tmt = treatment.

For the subgroup of patients without diabetes, approximately 55% to 60% of patients treated with one of the higher dose combination therapies (i.e., AML 10 mg + OM 10 mg, AML 10 mg + OM 20 mg, AML 5 mg + OM 40 mg, and AML 10 mg + OM 40 mg) reached their blood pressure goal.

The subgroup with diabetes, which started with a higher mean baseline blood pressure of 168.6/101.1, had a lower percentage of patients who reached their blood pressure goal. For the subgroup of patients with diabetes, approximately 10% to 13% of patients treated with one of the higher dose combination therapies (i.e., AML 10 mg + OM 10 mg, AML 10 mg + OM 20 mg, AML 5 mg + OM 40 mg, and AML 10 mg + OM 40 mg) reached their blood pressure goal.

Analysis by Race

The mean baseline SeDBP was 102.4 mm Hg for the subgroup of Black subjects and 101.4 mm Hg for the subgroup of non-Black subjects. For both race subgroups, each active treatment group had a statistically significant mean reduction in SeDBP from baseline to Week 8 with LOCF ($p<0.01$). The result of this subgroup analysis appear in Table 18, below.

Table 18: Mean Change in SeDBP (mm Hg) from Baseline to Week 8 with LOCF Stratified by Race (Black vs. non-Black) – Intent to Treat Population

	Black Subjects			Non-Black Subjects		
Treatment	N[1]	Change Mean ± SD	p-value[2]	N[1]	Change Mean ± SD	p-value[2]
Placebo	45	-1.3 ± 9.55	0.4587	115	3.8 ± 11.04	<0.0001
OM 10	32	-5.3 ± 8.44	0.0012	128	-9.0 ± 9.35	<0.0001
OM 20	34	-4.5 ± 9.98	0.0032	125	-10.5 ± 9.30	<0.0001
OM 40	44	-5.5 ± 9.51	<0.0001	116	-12.0 ± 10.61	<0.0001
AML 5	42	-8.3 ± 8.66	<0.0001	119	-9.7 ± 8.11	<0.0001
AML 10	39	-13.4 ± 8.40	<0.0001	124	-12.5 ± 8.22	<0.0001
AML 5/OM 10	34	-9.4 ± 6.94	<0.0001	129	-15.0 ± 7.20	<0.0001
AML 5/OM 20	43	-12.4 ± 9.17	<0.0001	117	-14.6 ± 9.00	<0.0001
AML 5/OM 40	38	-13.9 ± 8.35	<0.0001	119	-16.0 ± 8.06	<0.0001
AML 10/OM 10	43	-15.5 ± 8.45	<0.0001	118	-16.2 ± 8.71	<0.0001
AML 10/OM 20	46	-15.2 ± 7.92	<0.0001	112	-17.8 ± 8.01	<0.0001
AML 10/OM 40	34	-15.7 ± 9.05	<0.0001	127	-19.9 ± 8.68	<0.0001

[1]N was the number of subjects with values at both time points.
[2]Two-sided p-values were obtained from an Analysis of Covariance model with treatment, race subgroup, and treatment-by subgroup interaction as fixed effects and baseline blood pressure as a covariate.
AML = amlodipine, OM = olmesartan medoxomil, SD = standard deviation.

There was a general association between increases in dose and greater mean reductions in SeDBP across the treatment groups for both the Black and non-Black subgroups. Across the range of combination therapies, the non-Black subgroup had numerically greater mean reductions in SeDBP compared with the Black subgroup. For both race subgroups, the greatest mean reductions in SeDBP occurred in the cohort of subjects treated with AML 10 mg + OM 40 mg .

The mean baseline SeSBP was 163.9 mmHg for the subgroup of Black subjects and 163.8 mmHg for the subgroup of non-Black subjects. All active treatment groups had statistically significant ($p<0.05$) mean reductions in SeSBP from baseline to Week 8 with LOCF for both race subgroups. The results of this subgroup analysis appear in Table 19, below.

Table 19: Mean Change in SeSBP (mm Hg) from Baseline to Week 8 with LOCF Stratified by Race (Black vs. non-Black) – Intent to Treat Population

	Black Subjects			Non-Black Subjects		
Treatment	N[1]	Change Mean ± SD	p-value[2]	N[1]	Change Mean ± SD	p-value[2]
Placebo	45	-4.3 ± 21.29	0.2150	115	-5.0 ± 17.69	0.0017
OM 10	32	-6.0 ± 12.30	0.0322	128	-12.9 ± 15.62	<0.0001
OM 20	34	-5.5 ± 17.06	0.0139	125	-16.1 ± 14.84	<0.0001
OM 40	44	-8.2 ± 16.07	0.0008	116	-19.1 ± 15.83	<0.0001
AML 5	42	-11.9 ± 13.40	<0.0001	119	-15.9 ± 15.39	<0.0001
AML 10	39	-22.1 ± 15.12	<0.0001	124	-19.0 ± 16.93	<0.0001
AML 5/OM 10	34	-18.8 ± 12.53	<0.0001	129	-25.6 ± 14.02	<0.0001
AML 5/OM 20	43	-23.7 ± 12.57	<0.0001	117	-23.5 ± 15.66	<0.0001
AML 5/OM 40	38	-24.7 ± 13.84	<0.0001	119	-25.7 ± 15.01	<0.0001
AML 10/OM 10	43	-24.1 ± 16.10	<0.0001	118	-25.8 ± 14.45	<0.0001
AML 10/OM 20	46	-25.3 ± 13.76	<0.0001	112	-30.9 ± 17.59	<0.0001
AML 10/OM 40	34	-28.7 ± 14.85	<0.0001	127	-30.5 ± 16.22	<0.0001

[1]N was the number of subjects with values at both time points.
[2]Two-sided p-values were obtained from an Analysis of Covariance model with treatment, race subgroup, and treatment-by subgroup interaction as fixed effects and baseline blood pressure as a covariate.
AML = amlodipine, OM = olmesartan medoxomil, SD = standard deviation.

For both race subgroups, mean reductions in SeSBP were, in general, numerically greater in the combination therapy groups compared with the monotherapy groups. Across most combination therapies, the non-Black subgroup had numerically greater mean reductions in SeSBP compared with the Black subgroup. For both race subgroups, the greatest mean reductions in SeSBP occurred in the groups treated with AML 10 mg + OM 40 mg.

With respect to comparisons of combination therapy versus monotherapy for SeDBP and SeSBP (from baseline to Week 8 with LOCF) in the subgroup of non-Black patients, each combination therapy had a significantly greater mean reduction in SeDBP and SeSBP compared to both of its monotherapy components ($p<0.001$ for all comparisons).

For the subgroup of Black patients, not all comparisons of combination therapy versus monotherapy resulted in significantly greater reductions for mean change in SeDBP and SeSBP from baseline to Week 8 with LOCF. Table 20 provides results of the comparisons between combination therapy versus monotherapy for the subgroup of Black patients.

Table 20: Mean Change in SeDBP and SeSBP (mm Hg) from Baseline to Week 8 with LOCF – Combination Therapy Versus Monotherapy Comparisons – Black Patients

Treatment Comparison			SeDBP Difference (Tmt 1 – Tmt 2)		SeSBP Difference (Tmt 1 – Tmt 2)	
Tmt 1	**vs.**	**Tmt 2**	**LS Mean (SE)**	**p-value**	**LS Mean (SE)**	**p-value**
AML5/OM10	vs.	OM10	-4.0 (2.17)	0.0322	-13.1 (3.58)	0.0001
	vs.	AML5	-1.0 (2.03)	0.3066	-5.2 (3.36)	0.0605
AML5/OM20	vs.	OM20	-7.6 (2.02)	<0.0001	-16.6 (3.34)	<0.0001
	vs.	AML5	-4.1 (1.91)	0.0163	-9.3 (3.16)	0.0016
AML5/OM40	vs.	OM40	-8.5 (1.95)	<0.0001	-17.1 (3.22)	<0.0001
	vs.	AML5	-5.8 (1.97)	0.0018	-11.1 (3.26)	0.0004
AML10/OM10	vs.	OM10	-10.4 (2.05)	<0.0001	-19.7 (3.40)	<0.0001
	vs.	AML10	-2.0 (1.94)	0.1549	-1.9 (3.22)	0.2759
AML10/OM20	vs.	OM20	-10.8 (1.99)	<0.0001	-20.0 (3.29)	<0.0001
	vs.	AML10	-1.7 (1.91)	0.1851	-2.8 (3.17)	0.1848
AML10/OM40	vs.	OM40	-9.9 (2.01)	<0.0001	-19.9 (3.32)	<0.0001
	vs.	AML10	-1.7 (2.07)	0.2023	-3.9 (3.42)	0.1255

LS Mean, SE, 95% CI, and one-sided p-values were obtained from an Analysis of Covariance model with fixed effects for treatment, age group, and diabetic status, and baseline as a covariate.
AML = amlodipine, OM = olmesartan medoxomil, LS = least squares, SE = standard error, SeDBP = seated diastolic blood pressure, SeSBP = seated systolic blood pressure, Tmt = treatment.

For the subgroup of Black patients, approximately 38% to 51% of patients treated with one of the higher dose combination therapies (i.e., AML 10 mg + OM 10 mg, AML 10 mg + OM 20 mg, AML 5 mg + OM 40 mg, and AML 10 mg + OM 40 mg) reached their blood pressure goal.

For these same higher dose combinations, the subgroup of non-Black patients had a percentage of patients who reached their blood pressure goal that ranged from approximately 48% to 56%.

Generally, the response to all therapy groups, monotherapy and combination, was found to be greater in the non-Black population, except for the AML 10 mg monotherapy.

A Randomized, Double-Blind, Placebo-Controlled Factorial Study Evaluating The Efficacy And Safety of Co-Administration of Amlodipine Besylate Plus Olmesartan Medoxomil Compared to Monotherapy in Patients with Mild to Severe Hypertension (Long-Term, Open-Label Study Phase, United States)

Objectives: The main objective of the open-label Period III (Week 8 through Week 52) phase of the pivotal trial was to test long-term safety, and the durability of effect of co-administration of amlodipine (AML) and olmesartan medoxomil (OM) (plus the addition of hydrochlorothiazide [HCTZ], if needed) while minimally treating patients to blood pressure goal (<140/90 mm Hg, <130/80 mm Hg for diabetic patients). A further objective was to evaluate the number (percentage) of patients achieving blood pressure goal (defined as blood pressure <140/90 mm Hg, <130/80 mm Hg for diabetic patients).

Methodology: Period III consisted of a 44-week, open-label treatment period to assess long-term safety and efficacy of various treatment combinations. After completing Period II, all patients were switched to the combination of AML 5 mg + OM 40 mg. Those patients whose blood pressure was not adequately controlled (i.e., did not achieve a blood pressure goal of <140/90 mm Hg, or <130/80 mm Hg for those patients with diabetes) on AML 5 mg + OM 40 mg were titrated to AML 10 mg + OM 40 mg. Patients whose blood pressure was still not adequately controlled were additionally offered HCTZ 12.5 mg and subsequently 25 mg as required to achieve this blood pressure goal.

Safety assessments included adverse events, evaluation of edema, clinical laboratory measurements, vital signs, physical examinations, 12-lead ECG assessments, and special chemistry analytes.

Efficacy Results for the Open-Label Period: A total of 1684 patients entered Period III of the trial. After 2 weeks of the open-label treatment period (Week 10), 1640 patients remained on AML 5 mg + OM 40 mg with a mean SeDBP of 86.0 mmHg and a mean SeSBP of 137.9 mmHg. A total of 48.3% (792 of 1640) of patients on AML 5 mg + OM 40 mg reached their blood pressure treatment goal within 2 weeks of treatment. As patients were titrated to more intensive treatment regimens, an overall greater percentage of patients reached their blood pressure treatment goal.

From the mean baseline blood pressure of 163.6/101.5 mmHg from Period II, blood pressure reductions were observed across all combination treatment regimens to Week 52. At Week 52 or ET (early termination), the mean SeDBP in patients who remained on AML 5 mg + OM 40 mg was 81.0 mmHg and the mean SeSBP was 127.6 mmHg. A total of 80.0% of patients who remained on AML 5 mg + OM 40 mg achieved the blood pressure goal. For patients whose treatment regimen was titrated to more intensive antihypertensive regimens, mean SeDBP and SeSBP at Week 52 were slightly higher than for patients who remained on the AML 5 mg + OM 40 mg treatment regimen. Despite more intensive antihypertensive regimens, lower percentages of patients achieved blood pressure goals. The groups of patients who required titration of the amlodipine dose or the addition of hydrochlorothiazide were more severe hypertensive patients and/or were more resistant to the antihypertensive effects of treatment.

Table 21, below, presents the BP reductions observed at Week 52 or Early Termination, and the percentage of patients who achieved BP goal (i.e., <140/90 mm Hg or <130/80 for patients with diabetes) in Period III of this study. Note that HCTZ 12.5 mg or 25 mg was added to those patients who did not reach goal on one of the treatment regimens, or where edema persisted.

Table 21: SeSBP and SeDBP at Week 52/Early Termination and Blood Pressure Goal Rates

Treatment (mgs)	No. of Patients	Mean SeSBP (mmHg)	Mean SeDBP (mmHg)	% of Subjects Reaching BP Goal*
AML 5/OM 40	525	127.6	81.0	80.0
AML 10/OM 40	378	130.9	82.4	70.6
AML 10/OM 40 + HCTZ 12.5	287	130.7	81.0	66.6
AML 10/OM 40 + HCTZ 25	419	136.8	83.4	46.3

*<140/90 mmHg or <130/80 for patients with diabetes

Sixty-three (63) patients received other non-standard treatment regimens that included HCTZ 25 mg, AML 5 mg, AML 10 mg + OM 20 mg, AML 2.5 mg + OM 20 mg, AML 5 mg + OM 20 mg, AML 5 mg + OM 20 mg + HCTZ 12.5 mg, AML 10 mg + OM 20 mg + HCTZ 12.5 mg, AML 2.5 mg + OM 40 mg + HCTZ 12.5 mg, AML 5 mg + OM 40 mg + HCTZ 12.5 mg, and AML 5 mg + OM 40 mg + HCTZ 25 mg. Taken as a separate cohort, these patients had a mean SeDBP of 79.4 mmHg and a mean SeSBP of 126.2 mmHg, with 68.3% of these patients reaching their BP goal.

The treatment-to-goal approach used during the open-label treatment period resulted in an increase in the overall number and percentage of patients who reached their blood pressure goal over time. A total of 48.2% (792 of 1640 patients) reached their blood pressure goal at Week 10. By Week 52/ET, the total percentage who reached their blood pressure goal increased to 66.7% (1115 of 1672 patients).

Each titration to a more intensive treatment regimen resulted in additional mean reductions in seated blood pressure. Titration from AML 5 mg + OM 40 mg to AML 10 mg + OM 40 mg resulted in a mean seated blood pressure reduction of 7.3/4.8 mmHg. The addition of HCTZ 12.5 mg to the AML 10 mg + OM 40 mg combination resulted in a mean seated blood pressure reduction of 7.7/4.5 mmHg. A further reduction in seated blood pressure of 9.9/6.0 mmHg resulted from the titration in HCTZ from 12.5 mg to 25 mg for patients on the maximum-strength treatment regimen of AML 10 mg + OM 40 mg + HCTZ 25 mg.

Safety Results for the Open-Label Period: No new safety issues were identified during the course of this study with any of the combination therapies. During the open-label period, adverse events were experienced by 622 (37.0%) patients on AML 5 mg + OM 40 mg, 455 (40.5%) patients on AML 10 mg + OM 40 mg, 312 (42.4%) patients on AML 10 mg + OM 40 mg + HCTZ 12.5 mg, and 248 (56.4%) patients on AML 10 mg + OM 40 mg + HCTZ 25 mg.

Drug-related adverse events were experienced by 221 (13.2%) patients on AML 5 mg + OM 40 mg, 195 (17.3%) patients on AML 10 mg + OM 40 mg, 124 (16.8%) patients on AML 10 mg + OM 40 mg + HCTZ 12.5 mg, and 89 (20.2%) patients on AML 10 mg + OM 40 mg + HCTZ 25 mg.

Across all treatment regimens, most adverse events and drug-related adverse events were considered mild to moderate in severity. There were no apparent trends among the treatment groups with regard to the maximum severity of either adverse events or drug-related adverse events.

One patient on AML 10 mg + OM 40 mg died as a result of a gunshot wound to the head during the open-label treatment period. This death was not related to use of the study medication. Serious adverse events (SAEs) were experienced by 31 (1.8%) patients on AML 5 mg + OM 40 mg, 23 (2.0%) patients on AML 10 mg + OM 40 mg, 15 (2.0%) patients on AML 10 mg + OM 40 mg + HCTZ 12.5 mg, and 18 (4.1%) patients on AML 10 mg + OM 40 mg + HCTZ 25 mg. Four patients experienced SAEs while on non-standard treatment regimens. One patient on AML 5 mg + OM 40 mg had a drug-related SAE (non-cardiac chest pain).

A total of 77 (4.6%) patients were discontinued during the open-label treatment period due to an adverse event. Seventy (4.2%) patients were discontinued from the study for adverse events that started during the open-label treatment period. Adverse event discontinuations were experienced by 28 (1.7%) patients on AML 5 mg + OM 40 mg, 17 (1.5%) patients on AML 10 mg + OM 40 mg, 11 (1.5%) patients on AML 10 mg + OM 40 mg + HCTZ 12.5 mg, and 11 (2.5%) patients on AML 10 mg + OM 40 mg + HCTZ 25 mg. Three (3.5%) patients experienced an adverse event discontinuation while on a non-standard treatment regimen. Seven (0.4%) other patients were discontinued from the study during the open-label period for an adverse event that started during the double-blind treatment period. Thirty-five (2.1%) patients were discontinued due to drug-related adverse events.

A review of the frequency and specific types of events, as well as an assessment of potential relationships between the events and study medication, suggest that there was no greater incidence of SAEs or adverse event discontinuations due to the combination of OM and AML, or the combination of OM, AML, and HCTZ.

Edema (including the preferred terms of edema, edema peripheral, and pitting edema) was the most common drug-related adverse event and was experienced by a total of 318 (18.9%) patients. Across the 4 standard treatment regimens, the frequency of drug-related edema ranged from 7.0% to 11.1%. Dizziness (ranging from 1.4% to 2.0%) was the other most common drug-related, treatment-emergent adverse event.

In addition to assessing the incidence of adverse events categorized as edema, shifts in the severity of peripheral edema were also evaluated. Throughout the open-label treatment period, there appeared to be an approximate doubling in the frequency of patients with shifts toward worsening peripheral edema grade with AML 10 mg + OM 40 mg treatment (12.2%) compared to AML 5 mg + OM 40 mg treatment (7.2%). The apparent worsening in peripheral edema grade associated with the increased dose of amlodipine from 5 mg to 10 mg was somewhat ameliorated when HCTZ was added to the dosing regimen. The percentage of patients with shifts toward worsening peripheral edema grade was 10.3% for patients treated with AML 10 mg + OM 40 mg + HCTZ 12.5 mg, and 9.1% for patients treated with AML 10 mg + OM 40 mg + HCTZ 25 mg.

Overall, there was a low incidence of hypotension across the treatment regimens. Hypotension was experienced by 0.8% to 1.6% of patients on the 3 lowest dose treatment regimens and by 0.7% on AML 10 mg + OM 40 mg + HCTZ 25 mg.

There were no laboratory measurements that signaled a safety concern. Furthermore, there were no clinically meaningful changes in heart rates, ECGs, or physical examinations for any treatment group during the study.

Efficacy and Safety of Amlodipine Used as Add-On Therapy in Moderately to Severely Hypertensive Patients Not Adequately Controlled by Olmesartan Medoxomil 20 mg Monotherapy (Phase III, Europe)

Objectives: The primary objective was to demonstrate the additional antihypertensive efficacy in lowering trough sitting diastolic blood pressure (DBP) gained by adding amlodipine (AML) 5 mg or 10 mg to the treatment regimen in patients with hypertension not adequately controlled on olmesartan medoxomil (OM) 20 mg alone as assessed by conventional blood pressure (BP) measurements after 8 weeks of double-blind treatment. The primary efficacy endpoint was the mean change from baseline to the end of the double-blind treatment period, using last observation carried forward (LOCF) in trough sitting DBP.

The secondary objectives of this study consisted of an evaluation of the trough SeSBP after 4 weeks and 8 weeks of double-blind treatment in comparison to OM 20 mg. Additionally, SeDBP was also evaluated after 4 weeks of double-blind treatment. Ambulatory blood pressure monitoring (ABPM) was utilized to evaluate antihypertensive efficacy (daytime, nighttime, and 24 hour) in DBP and SBP after 8 weeks of treatment and blood pressure goal (defined as BP <140/90 mm Hg, <130/80 mmHg for diabetic patients) was also evaluated after 4 and 8 weeks of double-blind therapy. Lastly, safety and tolerability were assessed for the combinations of OM and AML versus monotherapy with OM 20 mg.

Methodology: This was a multi-center, multi-national, randomized, double-blind, parallel-group trial of 538 patients with moderate to severe hypertension (SBP ≥ 160 mm Hg and DBP ≥ 100 mm Hg) or not controlled on olmesartan monotherapy (BP ≥ 140/90 mm Hg). The study consisted of a 1-2 week taper off period for eligible patients previously on antihypertensive treatment (other than olmesartan monotherapy), followed by 16 weeks of active treatment. For the first 8 weeks (Period I), all patients received open-label once-daily doses of olmesartan 20 mg. At the end of the 8 weeks, only non-responders were then randomized to a double-blind, 8-week period (Period II) during which they received once-daily doses of placebo + OM 20 mg, AML 5 mg + OM 20 mg, or AML 10 mg + OM 20 mg. Patients controlled on olmesartan 20mg at the end of week 8 were discontinued from the study and not enrolled into the double-blind period.

The BP requirements for entering the open-label monotherapy treatment period included a mean sitting BP of ≥160/100 mm Hg, a mean 24-hour DBP of ≥84 mmHg, and at least 30% of daytime DBP readings >90 mm Hg. Patients treated with either OM 20 mg or OM 40 mg at the beginning of the trial had to have a mean sitting BP of ≥140/90 mm Hg, a mean 24-hour DBP of ≥80 mm Hg, and at least 30% of daytime DBP readings >85 mm Hg.

To enter the double-blind treatment period, patients needed to be non-responders to OM 20 mg. A non-responder was defined as mean trough sitting DBP ≥90 mm Hg; mean trough sitting SBP ≥140 mm Hg; and mean 24-hour DBP ≥80 mm Hg with at least 30% of daytime DBP readings >85 mm Hg. In addition to the BP requirements, patients should have met all other entry qualifications based on medical history, physical examination, electrocardiogram (ECG), and laboratory tests.

The Intent-to-Treat population (ITT) included all randomized patients who received at least 1 dose of double-blind study treatment and had at least 1 post-baseline efficacy assessment.

Sphygmomanometers were used for conventional BP measurements throughout the trial. After a 10-minute rest period, 3 separate sitting BP measurements were taken at least 1 minute apart. In addition, 24-hour ABPM was performed 3 times during the study (1 day prior to Visits 2, 4, and 6).

Safety assessments included adverse events, clinical laboratory measurements (hematology, biochemistry, and urinalysis), vital signs, physical examinations, and 12-lead ECG assessments.

Subgroup analyses were performed on the following subgroups: age (< 65 years, ≥ 65 years, ≥ 65 and < 75 years, and ≥ 75 years), gender (male, female), and hypertension severity (moderate or severe).

Efficacy Results: Of the 1,519 patients screened, 722 patients entered the open-label treatment period. There were 184 patients who discontinued from Period I, of which 148 patients were not eligible to continue to the double-blind treatment period. Therefore, a total of 538 patients were randomized in the double-blind treatment period. Of the 538 patients, 263 (48.9%) were male and all were Caucasian. The mean age was 56.8 years with 145 (27%) patients ≥ 65 years of age. A total of 43 (8.0%) patients had diabetes. Also, 68.6% of patients were classified with a BP of moderate severity and 26.2% were classified as severe. The treatment groups were similar with respect to BP

at the start of the open-label treatment period. For patients randomized in the double-blind treatment period, mean sitting BP was 170.9/104.3 at the beginning of the monotherapy period.

The primary efficacy analysis demonstrated that 8 weeks of double-blind treatment with the combination of AML + OM (AML 5 mg + OM 20 mg and AML 10 mg + OM 20 mg) reduced mean sitting DBP to a significantly greater extent than treatment with placebo + OM 20. Table 22 presents the results for mean change and adjusted mean change in SeDBP from baseline (week 8) to week 16 (end of double-blind treatment) with LOCF for the ITT population. Treatment with AML + OM combination therapy resulted in statistically significant reductions in adjusted mean sitting DBP when compared with placebo + OM 20 mg therapy.

Table 22: Mean Change in SeDBP (mm Hg) from Baseline (Week 8) to Week 16 with LOCF – ITT population

Week 16 LOCF Analysis Variable	**Placebo/OM20 (N = 179)**	**AML5/OM20 (N = 182)**	**AML10/OM20 (N = 177)**
N [1]	179	182	177
Baseline mean (SD) [2]	97.2 (4.89)	97.5 (4.34)	97.1 (4.22)
Week 16 LOCF mean (SD) [3]	89.4 (8.54)	86.9 (7.39)	86.0 (7.59)
Mean change (SD)	-7.8 (7.86)	-10.6 (7.20)	-11.1 (8.01)
Adjusted mean change (SE) [4]	-7.6 (0.55)	-10.4 (0.55)	-10.9 (0.56)
Treatment comparison with Placebo/OM20			
Adjusted mean change (SE) [4]		-2.7 (0.75)	-3.2 (0.76)
95% confidence interval [4]		-4.4, -1.1	-4.9, -1.5
P-value [4]		0.0006	<0.0001

1. N = the number of patients with values at both time points.
2. Baseline = Week 8.
3. Week 16 LOCF was defined as the last available measurement during the double-blind treatment period.
4. Statistics were based on an Analysis of Covariance model, including treatment, pooled centre, and baseline value as a covariate. All comparisons are with Placebo/OM20 using Dunnett's test to adjust for multiple testing. Adjusted means (least squares mean) and corresponding standard errors were derived from the ANCOVA model.

AML = amlodipine; LOCF = last observation carried forward; OM = olmesartan medoxomil; SD = standard deviation; SE = standard error.

Similar results, as shown in Table 23, were observed for adjusted mean sitting SBP, and 24-hour BP by ABPM. For mean sitting SBP, the adjusted mean change from baseline (week 8) to week 16 with LOCF was -10.2 mm Hg for the placebo + OM 20 mg treatment group, -16.1 mm Hg for the AML 5 mg + OM 20 mg treatment group, and -16.7 mm Hg for the AML 10 mg + OM 20 mg treatment group. Treatment with AML + OM combination therapy resulted in statistically significant reductions in adjusted mean sitting SBP from baseline (week 8) to week 16 with LOCF when compared with placebo + OM 20 mg therapy: -5.8 mm Hg for AML 5 mg + OM 20 mg ($p<0.0001$) and -6.4 mm Hg for AML 10 mg + OM 20 mg ($p<0.0001$).

Table 23: Mean Change in SeSBP (mm Hg) from Baseline (Week 8) to Week 16 with LOCF – ITT population

Week 16 LOCF Analysis Variable	Placebo/OM20 (N = 179)	AML5/OM20 (N = 182)	AML10/OM20 (N = 177)
N [1]	179	182	177
Baseline mean (SD) [2]	155.9 (10.26)	155.8 (10.12)	154.9 (9.79)
Week 16 LOCF mean (SD) [3]	145.3 (13.76)	139.5 (12.38)	138.4 (12.02)
Mean change (SD)	-10.6 (12.89)	-16.2 (10.66)	-16.5 (12.93)
Adjusted mean change (SE) [4]	-10.2 (0.86)	-16.1 (0.86)	-16.7 (0.87)
Treatment comparison with OM20/Placebo			
Adjusted mean change (SE) [4]		-5.8 (1.18)	-6.4 (1.18)
95% confidence interval [4]		-8.4, -3.2	-9.1, -3.8
P-value [4]		<0.0001	<0.0001

1. N = the number of patients with values at baseline and the given timepoint.
2. Baseline = Week 8.
3. Week 16 LOCF was defined as the Week 16 measurement or the last available measurement during the double-blind treatment period if the Week 16 value was missing.
4. Statistics are based on an Analysis of Covariance model, including treatment, pooled centre, and baseline value as a covariate. All comparisons are with OM20/Placebo using Dunnett's test to adjust for multiple testing. Adjusted means (least squares mean) and corresponding standard errors were derived from the ANCOVA model.

AML = amlodipine; LOCF = last observation carried forward; OM = olmesartan medoxomil; SD = standard deviation; SE = standard error.

The adjusted mean change from baseline (week 8) to week 16 in 24-hour mean ambulatory DBP was -4.5 mmHg for the placebo + OM 20 mg treatment group, -7.3 mmHg for the AML 5 mg + OM 20 mg treatment group, and -8.4 mmHg for the AML 10 mg + OM 20 mg treatment group. Treatment with AML + OM combination therapy resulted in statistically significant reductions in 24-hour adjusted mean ambulatory DBP from baseline (week 8) to week 16 LOCF when compared with placebo + OM 20 mg therapy: -2.8 mmHg for AML 5 mg + OM 20 mg (p=0.0031) and -3.9 mmHg for AML 10 mg + OM 20 mg (p<0.0001).

The adjusted mean change from baseline (week 8) to week 16 in 24-hour mean ambulatory SBP was -6.5 mmHg for the placebo + OM 20 mg treatment group, -11.4 mm Hg for the AML 5 mg + OM 20 mg treatment group, and -12.4 mm Hg for the AML 10 mg + OM 20 mg treatment group. Treatment with AML + OM combination therapy resulted in statistically significant reductions in 24-hour adjusted mean ambulatory SBP when compared with placebo + OM 20 mg therapy: -4.9 mm Hg for AML 5 mg + OM 20 mg (p=0.0020) and -5.8 mm Hg for AML 10 mg + OM 20 mg (p=0.0003).

Results were similar for mean changes in daytime mean DBP and SBP and nighttime mean DBP and SBP.

The adjusted mean change in SeDBP at Week 12 for patients treated with AML 10 mg + OM 20 mg combination therapy (-2.8 mm Hg) was statistically significant when compared to placebo + OM 20 mg therapy (p=0.0002). The adjusted mean change in sitting DBP at Week 12 for patients treated with AML 5 mg + OM 20 mg was -0.9 mm Hg when compared to placebo + OM 20 mg (p=0.3703). For SeSBP, the adjusted mean change for both the AML 5 mg + OM 20 mg treatment group (-2.9 mm Hg; p=0.0220) and the AML 10 mg + OM 20 mg treatment group (-6.3 mm Hg; p<0.0001) were statistically significant in comparison to the placebo + OM 20 mg. The time course of BP reductions demonstrated that in the group of patients that received AML 10 mg + OM 20 mg, earlier reductions in mean sitting DBP and SBP were achieved compared to patients that received AML 5 mg + OM 20 mg. At the week 12 visit, the difference in BP reduction between the placebo + OM 20 mg treatment group and the AML + OM combination treatment groups was greater in the AML 10 mg + OM 20 mg treatment group, compared to the AML 5 mg + OM 20 mg treatment group. However, with time, the differences between the 2 combination regimens narrowed and by week 16, the reductions in BP for both AML + OM combination treatment regimens were very similar.

The greater reductions in BP observed with AML and OM combination treatment translated into significantly more patients achieving pre-defined BP goals in both AML + OM combination treatment groups compared to the placebo + OM 20 mg treatment group. Compared to patients treated with placebo + OM 20 mg (28.5% achieving goal), the percentage of patients achieving BP goal at week 16 with LOCF was significantly higher in the AML 5 mg + OM 20 mg treatment group (44.5%; p=0.0011) and in the AML 10 mg + OM 20 mg treatment group (45.8%; p=0.0004).

In the subgroup analyses, the efficacy of the AML + OM combination treatment regimens compared to placebo + OM 20 mg was similar for all age groups, for both males and females, and for both categories of hypertension severity.

Safety Results:

There were no new safety issues identified during the course of this study with either placebo + OM 20 mg, AML 5 mg + OM 20 mg, or AML 10 mg + OM 20 mg.

A total of 38 (21.2%) patients on placebo + OM 20 mg therapy experienced a treatment-emergent adverse event (TEAE) during Period II; 16 (8.9%) of these patients were considered to have had a drug-related TEAE. Thirty-two (17.6%) patients on AML 5 mg + OM 20 mg therapy experienced a TEAE; 14 (7.7%) of these patients were considered to have had a drug-related TEAE. A total of 35 (19.8%) patients on AML 10 mg + OM 20 mg therapy experienced a TEAE; 20 (11.3%) of these patients were considered to have a drug-related TEAE by the Investigator. Across the 3 treatment groups, most TEAEs and drug-related TEAEs were considered mild in severity. The differences in the incidence of TEAEs or drug-related TEAEs were not considered clinically meaningful when comparing the AML + OM combination regimens to the placebo + OM 20 mg treatment group.

There did not appear to be any meaningful differences in the incidence of adverse events in the AML + OM combination regimens compared to the placebo + OM 20 mg treatment group. Outside of peripheral edema, which had a slightly higher incidence in the AML 10 mg + OM 20 mg treatment group, there were no clinically meaningful patterns of TEAE incidence that signified that there might be a safety issue in a particular treatment group.

Overall, the most commonly reported drug-related TEAEs in the placebo + OM 20 mg treatment group were headache (1.7%), dizziness (1.1%), and hyperkalemia (1.1%). The incidence of drug-related treatment-emergent peripheral edema in the OM 20 mg + placebo group was 0.6%. The most commonly reported drug-related TEAEs in the AML 5 mg + OM 20 mg treatment group were headache (3.3%), peripheral edema (1.1%), and hyperkalemia (1.1%). The most commonly reported drug-related TEAEs in the AML 10 mg + OM 20 mg treatment group were headache (2.3%), peripheral edema (2.3%), increased blood potassium (1.1%), and increased gamma-glutamyltransferase (γ-GT) (1.1%).

During Period II, 5 (0.9%) patients discontinued due to an adverse event: 2 patients from the placebo + OM 20 mg treatment group, of which 1 (pain in joints) was considered by the Investigator to be related to study medication; 1 patient from the AML 5 mg + OM 20 mg treatment group (dizziness) which was considered to be related to study medication by the Investigator; and 2 patients from the AML 10 mg + OM 20 mg treatment group; both of whom were considered by the Investigator to have had an event (peripheral edema) related to study medication.

There were no laboratory measurements that signified a safety concern. There were no clinically meaningful changes in potassium levels or in renal function in any of the 3 treatment groups. In the AML + OM combination regimens, there were similar increases in platelet counts; a decrease in platelet counts occurred in the placebo + OM 20 mg treatment group. These increases were not considered clinically meaningful. Furthermore, there were no clinically meaningful changes in heart rates, ECGs, or physical examinations when the combinations of AML and OM were compared to treatment with placebo + OM 20 mg.

Add-on Study of Olmesartan Medoxomil in Patients with Moderate to Severe Hypertension not Achieving Target Blood Pressure on Amlodipine 5 mg Alone (Phase III, Europe)

Objectives: The primary objective was to demonstrate the additional antihypertensive efficacy in lowering trough sitting diastolic blood pressure (DBP) gained by adding olmesartan medoxomil (OM) 10 mg, 20 mg, or 40 mg to the treatment regimen in patients with moderate to severe hypertension not adequately controlled on amlodipine (AML) 5 mg alone as assessed by conventional blood pressure (BP) measurements after 8 weeks of double-blind treatment. The primary efficacy endpoint was the mean change from baseline to the end of the double-blind treatment period, using last observation carried forward (LOCF) in trough sitting DBP.

The secondary objectives of this study consisted of an evaluation of the trough SeSBP from baseline (week 8) to week 12 and 16, from week 16 to week 20 and 24, and at week 28 and 34 in comparison to AML 5 mg. Additionally, SeDBP was evaluated from baseline to week 12, from week 16 to week 20 and 24, and at week 28 and 34. Ambulatory blood pressure monitoring (APBM) was utilized to evaluate antihypertensive efficacy (daytime, nighttime, and 24 hour) in DBP and SBP after 8 and 16 weeks of the double-blind treatment, and blood pressure goal (defined as BP <140/90 mmHg, <130/80 mmHg for diabetic patients) was evaluated during Period II, Period III, and Period IV (discussed below). The effect of titration to various dose combinations of AML and OM on DBP and SBP was evaluated. Safety and tolerability were assessed for the combinations of OM and AML versus monotherapy with AML 5 mg. Long-term safety and efficacy of the various combinations were also evaluated.

Methodology: This was a 52-week, randomized, parallel-group, multi-center, multi-national study consisting of 4 periods with patients who had hypertension (SBP ≥ 160 mm Hg and DBP ≥ 100 mm Hg) or were not controlled on amlodipine monotherapy (BP ≥ 140/90 mm Hg). For 8 weeks (Period I), patients received open-label once-daily doses of amlodipine 5 mg. Non-responders from Period I were then randomized to a double-blind, 8-week period (Period II) during which they received once-daily AML 5 mg + placebo, AML 5mg + OM 10mg, AML 5 mg + OM 20 mg, or AML 5 mg + OM 40 mg. A non-responder was defined as a patient with a mean trough sitting SBP and DBP ≥ 140/90 mmHg; and a mean 24-hour DBP ≥ 80 mmHg with at least 30% of daytime DBP readings >85 mm Hg. Patients who responded adequately to AML 5mg monotherapy during Period I were discontinued from the study. At week 16, patients with uncontrolled blood pressure (BP ≥ 140/90 mmHg) were titrated to higher doses for an additional double-blind 8-week period (Period III). Patients who had been randomized to combination therapy with AML 5mg + OM 10mg, AML 5 mg + OM 20 mg, and AML 5 mg + OM 40 mg had their doses titrated to AML 5mg + OM 20 mg, AML 5 mg + OM 40 mg, or AML 10 mg + OM 40 mg, respectively. Patients randomized to AML 5mg + placebo had their dose titrated to AML 5 mg + OM 20 mg. Patients controlled from Period II, continued on their assigned treatment regimen during Period III. At week 24, patients continued into a 28-week, open-label extension study (Period IV) during which they all received AML 5 mg + OM 40 mg once-daily. If blood pressure was not controlled (BP ≥ 140/90 mmHg), patients were titrated to AML 10 mg + OM 40 mg; if blood pressure was still not controlled, hydrochlorothiazide 12.5 mg or 25 mg were added.

Sphygmomanometers were used for conventional BP measurements throughout the trial. After a 10-minute rest period, 3 separate sitting BP measurements were taken at least 1 minute apart. In addition, 24-hour ABPM was performed 4 times during the study (1 day prior to the start of Periods I, II, III, and IV)

The Full Analysis Set 1 included all randomized patients who received at least 1 dose of double-blind study medication and had a baseline sitting DBP measurement and at least 1 post-randomization sitting DBP measurement during Period II. This analysis population comprised 746 of the 755 randomized patients in Period II. The Full Analysis Set 2 included all randomized patients who received at least 1 dose of double-blind study medication during Period III and had a sitting DBP measurement at week 16 and at least 1 sitting DBP measurement during Period III (week 20 and/or week 24).

Safety assessments included treatment-emergent adverse events (TEAEs), clinical laboratory test results, vital signs, physical examinations, and 12-lead ECG assessments.

Results: The results provided include data from Period I, II, and III and the interim results from Period IV based on all data through week 34 of the study.

In total, 1017 patients entered Period I and received AML 5 mg monotherapy. Of the 1017 patients, 755 (74.2%) completed Period I and 262 (25.8%) discontinued during Period I, or were withdrawn at the end of Period I because they were responders. A total of 755 patients were randomized into Period II. Of the 755 randomized patients, 49 (6.5%) discontinued and 706 (93.5%) completed Period II. Subsequently, 706

patients entered Period III, the double-blind up-titration period, of which 402 patients continued on their randomized treatment regimen from Period II, and 304 patients whose BP was not adequately controlled at the end of Period II had their doses titrated. For Period IV, 692 patients initially received AML 5 mg + OM 40 mg. As of week 34, 550 patients were on AML 5 mg + OM 40 mg, 120 patients were on AML 10 mg + OM 40 mg, 6 patients were on OM 40 mg + AML 10 mg + HCTZ 12.5 mg, and 1 patient was on OM 40 mg + AML 10 mg + HCTZ 25 mg.

The treatment groups for Period II were comparable with respect to demographic characteristics. Of the 755 patients, 61.1% were male, 99.7% were Caucasian, and the mean age was 55.8 years. Mean baseline BP was 164/102 mm Hg at the start of the study.

Table 24 presents the results for the primary efficacy parameter, the mean change in trough sitting DBP from baseline (Week 8) to Week 16 with LOCF (Period II), for the Full Analysis Set 1. Compared with placebo + AML 5 mg, treatment with OM + AML resulted in statistically significant reductions in sitting DBP.

Table 24: Mean Change in Sitting Diastolic Blood Pressure – Period II

Time Point Statistic	AML5/Placebo (N = 184)	AML5/OM 10 (N = 189)	AML5/OM20 (N = 187)	AML5/OM40 (N = 186)
Week 16 LOCF				
N [1]	184	189	187	186
Baseline mean (SD) [2]	97.2 (5.03)	96.9 (5.37)	96.9 (5.10)	97.0 (4.96)
Week 16 LOCF mean (SD) [3]	91.5 (8.39)	89.5 (7.58)	87.6 (8.63)	87.5 (7.22)
Mean change (SD)	-5.7 (7.66)	-7.4 (7.14)	-9.3 (7.74)	-9.5 (6.64)
Adjusted mean change (SE) [4]	-5.7 (0.53)	-7.7 (0.52)	-9.5 (0.52)	-9.6 (0.52)
Treatment comparison with AML5/Placebo				
Adjusted mean change (SE) [4]		-2.0 (0.73)	-3.7 (0.73)	-3.8 (0.73)
Adjusted 95% confidence interval [4]		(-3.7 , -0.2)	(-5.4 , -2.0)	(-5.5 , -2.1)
Adjusted p-value [4]		0.0207	<0.0001	<0.0001

1. N = number of patients with values at both baseline and the specified time point.
2. Baseline was the Visit 4 (Week 8) measurement.
3. Week 16 with LOCF was the Week 16 measurement, or the last available measurement during Period II if the Week 16 value was missing.
4. Statistics are from an Analysis of Covariance (ANCOVA) model with treatment and centre as effects and baseline as a covariate. Adjusted p-value is from Dunnett's test.

AML = amlodipine; LOCF = last observation carried forward; OM = olmesartan medoxomil; SD = standard deviation; SE = standard error.

Treatment with AML + OM (all evaluated dose regimens) demonstrated statistically significantly larger mean reductions in sitting DBP than placebo + AML 5 mg treatment at both the Week 12 and Week 16 time points. The DBP-lowering effect of AML 5 mg + OM 40 mg treatment was realized earlier than that of AML 5 mg + OM 20 mg treatment. At Week 16, the 2 highest dose regimens (AML 5 mg + OM 20 mg and AML 5 mg + OM 40 mg) demonstrated numerically larger mean reductions in sitting DBP than AML 5 mg + OM 10 mg.

Table 25 presents the results for the mean change in trough sitting SBP from baseline (Week 8) to Week 16 with LOCF (Period II) for the Full Analysis Set 1. Compared with AML 5 mg + placebo, treatment with AML + OM resulted in statistically significant reductions in sitting SBP.

Table 25: Mean Change in Sitting Systolic Blood Pressure – Period II

Time Point Statistic	AML5/Placebo (N = 184)	AML5/OM10 (N = 189)	AML5/OM20 (N = 187)	AML5/OM40 (N = 186)
Week 16 LOCF				
N [1]	184	189	187	186
Baseline mean (SD) [2]	155.2 (11.53)	154.6 (10.29)	154.0 (11.32)	153.7 (10.21)
Week 16 LOCF mean (SD) [3]	145.3 (14.26)	141.5 (12.84)	138.7 (14.45)	137.0 (13.23)
Mean change (SD)	-9.9 (12.43)	-13.1 (11.64)	-15.3 (13.32)	-16.7 (12.00)
Adjusted mean change (SE) [4]	-9.7 (0.88)	-13.2 (0.87)	-15.4 (0.87)	-16.8 (0.87)
Treatment comparison with AML5/Placebo				
Adjusted mean change (SE) [4]		-3.5 (1.21)	-5.8 (1.22)	-7.1 (1.22)
Adjusted 95% confidence interval [4]		(-6.4 , -0.7)	(-8.6 , -2.9)	(-10.0 , -4.3)
Adjusted p-value [4]		0.0103	<0.0001	<0.0001

1. N = number of patients with values at both baseline and the specified time point.
2. Baseline was the Visit 4 (Week 8) measurement.
3. Week 16 with LOCF was the Week 16 measurement, or the last available measurement during Period II if the Week 16 value was missing.
4. Statistics are from an Analysis of Covariance (ANCOVA) model with treatment and centre as effects and baseline as a covariate. Adjusted p-value is from Dunnett's test.

AML = amlodipine; LOCF = last observation carried forward; OM = olmesartan medoxomil; SD = standard deviation; SE = standard error.

Table 26 summarizes the percentage of patients in each treatment group who reached BP goal during Period II for the Full Analysis Set 1. Compared with AML 5 mg + placebo, treatment with AML + OM resulted in a statistically significantly higher proportion of patients who reached BP goal at Week 16 with LOCF.

Table 26: Number (%) of Patients Who Reached Blood Pressure Goal – Period II

Time Point BP Goal Achieved	AML5/Placebo (N = 184) n (%)	AML5/OM10 (N = 189) n (%)	AML5/OM20 (N = 187) n (%)	AML5/OM40 (N = 186) n (%)
Week 16 LOCF				
Yes	55 (29.9)	74 (39.2)	100 (53.5)	94 (50.5)
P-value [1]		0.0286	<0.0001	<0.0001

1. The Cochran-Mantel-Haenszel test, stratified by centre, was used to compare the percentages for combination therapies with placebo + AML 5 mg therapy.

AML = amlodipine; LOCF = last observation carried forward; OM = olmesartan medoxomil.

The results for mean changes in ambulatory BP during Period II support the results for mean changes in sitting BP during Period II.

Table 27 presents the results for mean changes in trough sitting DBP and SBP during Period III for the Full Analysis Set 2. For patients who remained on their randomized treatment regimen during Period III, mean changes in sitting DBP and SBP from Week 16 to Week 24 with LOCF were not meaningful. Titration resulted in further mean reductions in sitting DBP and SBP during Period III.

Table 27: Mean Changes in Sitting Blood Pressure – Period III

Treatment	N [1]	Mean Change (SD) in DBP	Mean Change (SD) in SBP	n (%) to BP goal
AML5/Placebo	68	0.7 (6.75)	1.0 (10.11)	40 (58.8)
AML5/Placebo to AML5/OM20	107	-8.2 (6.55)	-12.6 (11.47)	41 (38.3)
AML5/OM10	97	-0.7 (5.99)	-0.9 (9.39)	72 (74.2)
AML5/OM10 to AML5/OM20	82	-5.6 (7.02)	-7.5 (10.42)	23 (28.0)
AML5/OM20	118	-0.2 (6.76)	-0.9 (9.26)	89 (75.4)
AML5/OM20 to AML5/OM40	58	-6.2 (7.47)	-10.6 (12.76)	21 (36.2)
AML5/OM40	117	-0.6 (6.37)	-0.4 (9.39)	86 (72.9)
AML5/OM40 to AML10/OM 40	57	-8.2 (7.34)	-12.3 (11.12)	27 (47.4)

N = number of patients with values at both Week 16 and Week 24 with LOCF.
AML = amlodipine; BP = blood pressure; DBP = diastolic blood pressure; LOCF = last observation carried forward; OM = olmesartan medoxomil; SBP = systolic blood pressure; SD = standard deviation.

For patients who remained on their randomized treatment regimen during Period III, the proportion who reached BP goal at Week 24 with LOCF was higher with AML + OM treatment than with AML 5 mg + placebo treatment. For patients whose dose regimen was titrated, successively higher proportions reached BP goal with each increase in dose combination of AML + OM. The results for mean changes in ambulatory BP during Period III support the results for mean changes in sitting BP during Period III.

In total, 692 patients entered the open-label Period IV and initially received AML 5 mg + OM 40 mg. For the 563 patients on AML 5 mg + OM 40 mg at Week 34 or Early Termination, the mean sitting DBP was 83.6 mm Hg and the mean sitting SBP was 132.2 mm Hg. For the 121 patients on AML 10 mg + OM 40 mg at Week 34 or Early Termination, the mean sitting DBP was 90.3 mmHg and the mean sitting SBP was 143.0 mmHg. For the 6 patients on AML 10 mg + OM 40 mg + HCTZ 12.5 mg at Week 34 or Early Termination, the mean sitting DBP was 89.3 mm Hg and the mean sitting SBP was 147.6 mm Hg. For the 1 patient on AML 10 mg + OM 40 mg + HCTZ 25 mg at Week 34 or Early Termination, sitting DBP was 92.0 mm Hg and sitting SBP was 155.3 mm Hg.

Titration from AML 5 mg + OM 40 mg to AML 10 mg + OM 40 mg during Period IV resulted in a mean reduction in sitting DBP of 5.0 mm Hg and a mean reduction in sitting SBP of 8.7 mm Hg. Titration from AML 10 + OM 40 mg to AML 10 mg + OM 40 mg + HCTZ 12.5 mg resulted in a mean reduction in sitting DBP of 3.7 mm Hg and a mean reduction in sitting SBP of 3.1 mm Hg.

Of the 692 patients exposed to AML 5 mg + OM 40 mg during Period IV, 502 (72.5%) reached BP goal. Of the 127 patients exposed to AML 10 mg + OM 40 mg, 46 (36.2%) reached BP goal. Of the 6 patients exposed to AML 10 mg + OM 40 mg + HCTZ 12.5 mg, 2 (33.3%) reached BP goal. The 1 patient exposed to AML 10 mg + OM 40 mg + HCTZ 25 mg did not reach BP goal.

Safety Results: The incidence of TEAEs during double-blind treatment was similar for the treatment groups. During Period II, 175 (23.2%) patients had a TEAE: 42 (22.3%) in the AML 5 mg + placebo group, 48 (25.1%) in the AML 5 mg + OM 10 mg group, 39 (20.6%) in the AML 5 mg + OM 20 mg group, and 46 (24.6%) in the AML 5 mg + OM 40 mg group. Fifty-three (7.0%) patients had a TEAE that was considered by the investigator to be related to study treatment: 15 (8.0%) in the AML 5 mg + placebo group, 13 (6.8%) in the AML 5 mg + OM 10 mg group, 11 (5.8%) in the AML 5 mg + OM 20 mg group, and 14 (7.5%) in the AML 5 mg + OM 40 mg group. Most of the TEAEs were mild or moderate in severity. The distributions of TEAEs by maximum severity were similar for the treatment groups.

During Period II, the most frequently reported TEAEs in the AML 5 mg + placebo group were peripheral edema (2.1%) and vertigo (2.1%). The most frequently reported TEAEs in the AML 5 mg + OM 10 mg group were headache (3.1%) and dizziness (3.1%). The most frequently reported TEAEs in the AML 5 mg + OM 20 mg group were back pain (2.6%), dizziness (1.6%), and influenza (1.6%). The most frequently reported TEAEs in the AML 5 mg + OM 40 mg group were headache (3.7%) and dizziness (3.2%). During Period II, the most frequently reported drug-related TEAEs in the AML 5 mg + placebo group were peripheral edema (2.1%) and vertigo (1.1%). The most frequently reported drug-related TEAEs in the AML 5 mg + OM 10 mg group were headache (1.6%) and dizziness (1.6%). The most frequently reported drug-related TEAEs in the OM 20 mg + AML 5 mg group were peripheral edema (1.1%), dizziness (1.1%), and hypotension (1.1%). The most frequently reported drug-related TEAEs in the AML 5 mg + OM 40 mg group were headache

(2.7%) and dizziness (1.6%). The incidence of drug-related treatment-emergent peripheral edema in AML 5 mg + OM 40 group was 1.1%.

No patients died during Period II. Four (0.5%) patients had a serious adverse event (SAE) during Period II, however none of the SAEs were considered by the investigator to be related to study treatment.

Thirteen (1.7%) patients discontinued from the study during Period II due to a drug-related TEAE: 1 (0.5%) patient in the AML 5 mg + placebo (malaise), 3 (1.6%) patients in the AML 5 mg + OM 10 mg group (1 patient with dizziness and headache, 1 patient with decreased blood pressure, and 1 patient with vomiting and lethargy), 4 (2.1%) patients in the AML 5 mg + OM 20 mg group (1 patient with hypotension, 1 patient with myalgia, 1 patient with increased blood pressure, and 1 patient with peripheral edema), and 5 (2.7%) patients in the AML 5 mg + OM 40 mg group (1 patient with vertigo, 1 patient with dizziness, 2 patients with hypotension, and 1 patient with cold sweat, asthenia, and dizziness).

During Period III, 117 (16.6%) patients had a TEAE. No meaningful differences among the treatment regimens in the incidence of TEAEs during Period III were observed. Thirty-two (4.5%) patients had a TEAE that was considered by the investigator to be related to study treatment. Most of the TEAEs were mild or moderate in severity. The distributions of TEAEs by maximum severity were similar for patients on the various treatment regimens.

Four (0.6%) patients had an SAE during Period III, however, none of the SAEs were considered by the investigator to be related to study treatment. Two (0.3%) patients discontinued from the study during Period III due to a TEAE: 1 (0.8%) patient on AML 5 mg + OM 20 mg and 1 (0.8%) patient on AML 5 mg + OM 40. The TEAEs that led to discontinuation for the 1 (0.8%) patient on AML 5 mg + OM 40 mg (fatigue, angina pectoris, dizziness, headache, and visual disturbance) were considered by the investigator to be related to study treatment.

During Period IV through Week 34, a total of 37 (5.3%) patients had a TEAE that was considered by the investigator to be related to study treatment: 32 (4.6%) patients on AML 5 mg + OM 40 mg and 5 (3.9%) patients on AML 10 mg + OM 40 mg. Most of the TEAEs were mild or moderate in severity. The distribution of TEAEs by maximum severity was similar for patients on the various treatment regimens.

No patients died during Period IV. Seven (1.0%) patients had an SAE during Period IV, however, none of the SAEs were considered by the investigator to be related to study treatment.

Six (0.9%) patients discontinued from the study during Period IV due to a TEAE: 5 (0.7%) patients on AML 5 mg + OM 40 mg and 1 (0.8%) patient on AML 10 mg + OM 40 mg. For 4 (0.6%) patients on AML 5 mg + OM 40 mg, the TEAE that led to discontinuation was considered by the investigator to be related to study treatment (3 patients with dizziness and 1 patient with hypotension).

Mean changes in laboratory parameters and shifts in laboratory abnormalities were not clinically meaningful for any of the treatment groups during Period II or patients on the various treatment regimens during Periods III and IV. No clinically meaningful differences in these parameters between AML + OM combination treatment and AML + placebo treatment were noted. In addition, mean changes in pulse rate and ECG parameters during the study were not clinically meaningful. No clinically meaningful differences in these parameters were observed among the various treatment regimens. No clinically meaningful physical examination findings were noted, as well.

B. PUBLISHED AMLODIPINE/OLMESARTAN MEDOXOMIL ABSTRACTS

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A Randomized, Double-Blind, Placebo-Controlled Factorial Study Evaluating The Efficacy And Safety Of Co-Administration Of Amlodipine Besylate (AML) Plus Olmesartan Medoxomil (OM) Compared To Monotherapy In Patients (Pts) With Mild To Severe Hypertension (HTN)

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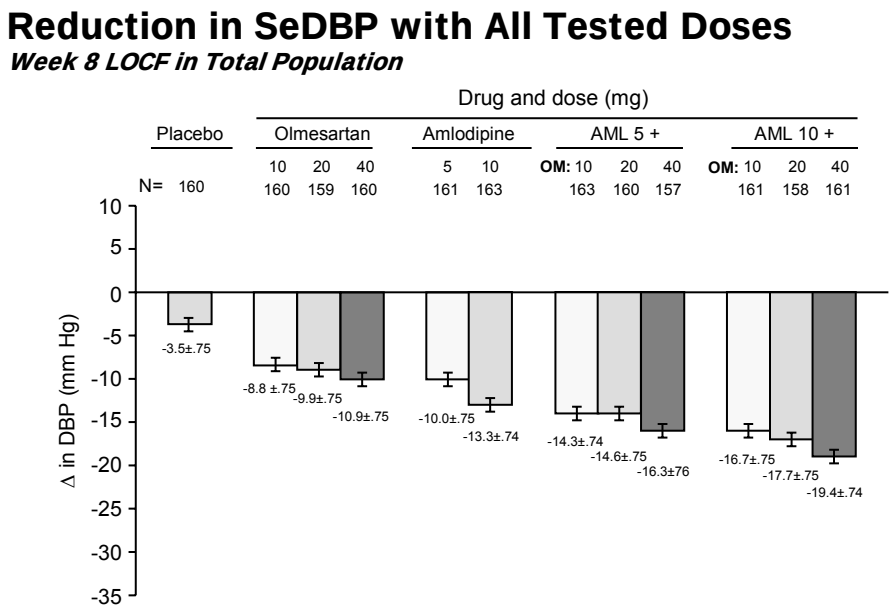
Most pts will need ≥2 antihypertensive agents to attain a blood pressure (BP) goal of <140/90 mmHg. Concomitant administration of the calcium channel blocker AML and the angiotensin receptor blocker OM has the potential to improve BP-lowering efficacy without additional safety concerns. We conducted a randomized, double-blind, placebo-controlled factorial study in 1940 pts with mild to severe HTN, defined as seated diastolic BP (SeDBP) between ≥95 mmHg and ≤120 mmHg, to determine if co-administration of AML 5-10 mg/day and OM 10-40 mg/day for 8 weeks has a significant benefit versus respective monotherapy components. Primary and secondary endpoints were mean change from baseline in SeDBP and seated systolic BP (SeSBP), respectively, at week (Wk) 8, with last observation carried forward if pts withdrew prior to Wk 8. Each combination had significantly greater reductions in SeDBP (Fig.) and SeSBP compared with both of its monotherapy components (P<0.0001 for all comparisons). The greatest observed mean reductions in seated SeSBP and SeDBP occurred with AML 10mg + OM 40mg (–30.1/–19.0 mmHg vs –4.8/–3.1 mmHg with placebo, and vs –19.7/–12.7 mmHg with AML 10 mg). Adverse event (AE) incidence for the AML + OM combination treatment groups was 52.7% (511/970 pts); the AE incidence in the placebo group was 56.2% (91/162 pts). Most AEs were mild in intensity. The AE profile for each of the combinations was similar in nature to the monotherapy components. In conclusion, the combination of AML + OM produced greater reductions in BP compared with placebo and respective monotherapy. BP reductions were dose-related and all regimens were well tolerated.

Figure



Values are expressed as LS mean ± SE. *P*<0.0001 for all active treatment groups.
AML or amlodipine=amlodipine besylate; LOCF=last observation carried forward; OM or olmesartan=olmesartan medoxomil; SeDBP=sitting diastolic blood pressure. Baseline diastolic blood pressure (DBP) = 101.6 mm Hg for safety population.

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A Fixed-Dose Combination of Olmesartan Medoxomil (OM) and Amlodipine Besylate (AM) is Bioequivalent (BEQ) to Free Combination of the Agents

Stephen Haworth, MD[1]; Mohinder Singh Bathala, PhD[1]; James Lee, PhD[1]; Mark Allison, MD[2]; Shashank Rohatagi, PhD[1]; Jean-Francois Marier, PhD[3]; Igor Rubets, PhD[3]; Daniel Salazar, PhD[1]

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The combination of an angiotensin receptor blocker and calcium channel blocker may have additive BP-lowering effects vs either monotherapy due to complementary mechanisms of action. A fixed-dose combination of OM + AM offers the potential for increased BP-lowering, convenient dosing, and improved compliance. The pharmacokinetics/bioavailability of a novel fixed-dose combination were assessed in a phase I study; 28 healthy subjects enrolled in a single-dose, open-label, 2-way crossover study were randomized in each dosing period to receive under fasting conditions the test treatment, a fixed-dose combination of OM/AM 40/10mg, or the reference treatment of free combination of OM 40mg and AM 10mg. Results showed the fixed-dose and free combinations were BEQ as the criteria of the 90% CI for the area under the concentration-time curve from time 0 to time t (AUC_{0-t}), AUC from time 0 to infinity ($AUC_{0-\infty}$) and C_{max} ratios (Test/Reference) for OM and AM were within 80.0 to 125.0% limit. [table1] All doses were well tolerated. Mean terminal elimination half-life ($t_{½}$) was similar after the test and reference treatments for OM (11h and 12h respectively) and AM (54h and 52h respectively). Of the 30 mild treatment-emergent AEs in 11 subjects (most frequently headache), 11 were possibly drug-related occurring in 4 subjects in the test and 2 subjects in the reference treatment groups. No clinically significant trends in abnormal laboratory findings occurred. The fixed-dose combination of OM/AM 40/10mg is BEQ to OM 40mg and AM 10mg coadministered separately.

Table

Parameter	Geometric LSM			
	Test [T] (n=26)	Reference [R] (n=27)	LSM ratio (T/R)	90% CI
OM				
AUC_{0-t} (ng·h/mL)	5374.2	5418.6	99.2	93.4, 105.3
$AUC_{0-\infty}$ (ng·h/mL)	5407.5	5468.3	98.9	93.2, 104.9
C_{max} (ng/mL)	833.3	810.3	102.9	94.8, 111.6
AM				
AUC_{0-t} (ng·h/mL)	424.8	410.9	103.4	100.1, 106.8
$AUC_{0-\infty}$ (ng·h/mL)	505.3	482.2	104.8	100.8, 109.0
C_{max} (ng/mL)	7.6	7.4	103.9	99.9, 108.2
LSM=least squares mean; t=time to last measurable concentration.				

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The Bioavailability (BAV) of a Fixed-Dose Combination of Olmesartan Medoxomil (OM) and Amlodipine Besylate (AM) is Unaffected by Food

Stephen Haworth, MD[1]; Reinilde Heyrman, MD[1]; Mohinder Singh Bathala, PhD[1]; James Lee, PhD[1]; Robert Noveck, MD, PhD[2]; Shashank Rohatagi, PhD[1];Jean-Francois Marier, PhD[3]; Igor Rubets, PhD[3]; Daniel Salazar, PhD[1]

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Most patients require ≥2 antihypertensive agents to achieve BP control. The combination of an angiotensin receptor blocker, e.g., OM, and a calcium channel blocker, e.g. AM, may provide increased BP-lowering efficacy compared with either monotherapy and a fixed-dose formulation of these agents simplifies dosing and may increase compliance. This study evaluated the effect of food on the BAV of an OM/AM fixed-dose combination using a randomized, open-label, 2-way crossover study in 28 healthy subjects who received a single fixed dose of OM/AM 40/10mg 30 min after a high-fat breakfast (treatment A) and after 10-hr fasting conditions (treatment B), with a 21-day washout period between treatments. Absence of a food effect was concluded if the 90% CIs for the treatment A:treatment B ratios for the geometric least squares mean of AUC time 0 to t (AUC_{0-t}), AUC time 0 to infinity ($AUC_{0-\infty}$) and C_{max} of AM and OM were 80-125.0%. All dosing regimens were well tolerated. Ratios of LSM of AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} for OM were 87%, 88%, 94%, with 90% CIs all within 80-125%. For AM, ratios of LSM of AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} were 103%, 103%, 99%, with 90% CIs all within 80-125%. The mean terminal elimination half-life for OM (14h) and AM (40h) was unaffected by food. Most treatment-emergent adverse events were of mild severity, occurring in 5 subjects. The only drug-related AE was headache (2 subjects). In conclusion, the BAV of OM and AM after a single fixed-dose combination tablet was equivalent either with food or under fasting conditions.

Table

Parameter	Geometric LSM			
	Treatment A - OM/AM 40/10mg (n=28) Fed	Treatment B - OM/AM 40/10mg (n=27) Fasting	LSM ratio [A/B] (%)	90%CI (%)
OM				
AUC_{0-t} (ng·h/mL)	5259.6	6034.3	87	82.5, 92.1
$AUC_{0-\infty}$ (ng·h/mL)	5366.5*	6111.7	88	83.0, 92.9
C_{max} (ng/mL)	881.9	939.5	94	87.4, 100.8
AM				
AUC_{0-t} (ng·h/mL)	307.0	299.2	103	99.6, 105.7
$AUC_{0-\infty}$ (ng·h/mL)	334.3	326.1	103	99.2, 106.0
C_{max} (ng/mL)	6.4	6.4	99	96.0, 102.7

LSM=least squares mean; *n=27

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Safety and Tolerability of the Combination of Olmesartan Medoxomil (OM) and Amlodipine Besylate (AM)

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Many hypertensive patients need >1 antihypertensive agent; combining agents with different mechanisms of action may improve efficacy vs monotherapy. The pharmacokinetics of a novel fixed-dose combination of OM and AM were compared with free combination of these agents (OM + AM) or monotherapy in phase 1 studies in 200 healthy volunteers (VOLS). Safety/tolerability data for OM/AM single- or multiple-dose studies of randomized, open-label, crossover design are presented. [table1] Most treatment-emergent adverse events (TEAEs) were of mild severity; the most common was headache. In one large study (Study 112; n=60), the most frequent TEAEs were headache, dizziness, cough and pharyngolaryngeal pain, reported in 37%, 13%, 12% and 12% of VOLS. In 2 studies (111, 110), headache was the only possibly drug-related AE; headache and dizziness were the only possibly or probably drug-related AEs in Study 112. There were no severe AEs for the fixed or free dose combination of OM + AM. 1 VOL given a single dose of OM 40mg + AM 10mg discontinued due to a non-drug related AE (Study 111). In Study 109, a VOL discontinued due to a positive serum pregnancy test and later had a spontaneous abortion classified as a serious, unlikely drug-related AE. There were few clinically significant laboratory abnormalities (0–6 VOLS in individual studies) and only 1 treatment-related laboratory abnormality (elevated liver enzymes) in 1 VOL. Generally, there were no clinically significant ECG abnormalities. The fixed-dose combinations of OM/AM appear to be safe and well tolerated in healthy VOLS.

Table

Regimen (mg)	**n**	**TEAE, # VOLS**	**Drug related AE, # VOLS‡**
Study 101			
OM 40+AM 10	24	8	5*
OM 40	23	10	7*
AM 10	23	14	7*
Study 111			
OM/AM 10/5	30	7	3*
OM/AM 40/10	29	3	1*
OM 10+AM 5	30	5	0*
OM 40+AM 10	29	3	0*
Study 112			
OM/AM 40/10	30	15	7¶
OM/AM 20/5	29	12	5¶
OM/AM 10/10	29	11	7¶
OM/AM 40/5	30	9	5¶
OM/AM 20/10	29	10	5¶
OM/AM 10/5	30	12	5¶
Study 110			
OM/AM 40/10	28	5	2*
Study 109			
OM/AM 40/10	27	6	4*
OM 40+AM 10	27	5	2*
***Possibly; ¶Possibly or Probably** ‡Pts can appear in >1 group within a study			

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Evaluation of Population (POP) Pharmacokinetics (PK) After Coadministration of Olmesartan Medoxomil (OM) and Amlodipine Besylate (AM)

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A novel fixed-dose combination of OM and AM may increase efficacy over monotherapy in patients (pts) with hypertension (HTN). The single formulation may also improve ease of administration and potentially compliance. Data from phase I studies in 170 healthy volunteers (HV) (studies CS8663-U101, 110, 111, 112) and from a subset (n≈546) of pts with HTN in a phase III trial (CS8663-U301) were used to make POP PK models and subsequent analyses of OM and AM. Both OM and AM were characterized by 1st order elimination/absorption and an absorption time lag in a 2 compartmental model for OM and a 1 compartmental model for AM. In the OM model, covariate analyses indicated decreased oral clearance (CL) for pts with HTN vs HV, female pts, pts with higher baseline serum creatinine (SeCr) vs lower SeCr or those with lower vs higher bodyweight (WT). For AM, CL decreased for pts with higher vs lower baseline ALT, older vs younger pts or pts with lower vs higher WT (Table). Gender-based differences were independent of WT and other covariates. Similarly, the association between age and AM exposure was due to an effect on AM CL that was independent of age-related changes in WT or other covariates. Combination therapy did not modify the effects of covariate status on CL of OM or AM. In conclusion, neither compound had a clinically significant impact on the CL of the other. The impact of covariates on the CL of OM and AM did not change between monotherapy and combination therapy.

Table

	POP mean	
	Estimate	Coefficient of variation [100□$SE_{estimate}$/estimate] (%)
OM		
CL_{TYP} (L/h)	5.9	4.4
V (L)	32.1	2.5
Ka (per h)	2.0	5.1
ALAG1 (h)	0.374	1.5
CL_{HV}	1.7	20
CL_{SEX}	-0.878	34
CL_{WT}	0.326	31
CL_{SeCr}	-0.278	25
AM		
CL_{TYP} (L/h)	22.9	1.7
V (L)	1530	2.0
Ka (per h)	0.640	2.3
ALAG1 (h)	0.390	10
CL_{WT}	0.207	36
CL_{AGE}	-0.373	14
CL_{ALT}	-0.138	32
ALAG1=absorption lag time; CL_{TYP}=oral CL of typical pt; K_a=absorption rate constant; V=volume of central distribution. Effects on CL are linear for discrete covariates, CL (HV)=CL_{TYP}+CL_{HV}, and multiplicative for continuous covariates, CL (WT of 90)=CL_{TYP} * ($90/WT_{median}$)^CL_{WT}		

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Olmesartan Medoxomil (OM) and Amlodipine Besylate (AM) Show Dose-Proportional Drug Exposure When Used in Combination in Healthy Volunteers (VOLS)

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JNC 7 recommends combination drug therapy if BP is >20/10mmHg above goal. In accordance, a fixed-dose combination of the angiotensin receptor blocker OM and the calcium channel blocker AM is being evaluated for antihypertensive efficacy. This study assessed the dose-proportionality of OM/AM fixed-dose combinations in VOLS in 2 cohorts of a randomized, open-label, 3-way crossover design. VOLS received a single dose of oral OM/AM under fasting conditions as follows: 40/10mg (treatment A), 20/5mg (B) and 10/10mg (C) in cohort 1 (n=30) or 40/5mg (D), 20/10mg (E) and 10/5mg (F) in cohort 2 (n=30). All dosing regimens were well tolerated. Noncompartmental pharmacokinetics (PK) by dose level (data pooled across treatments) are presented. [table1] A dose-proportional increase in OM AUC_{0-t} and $AUC_{0-\infty}$ was observed as the 95% CI of the regression coefficient for the ln-transformed PK parameters were within 0.75-1.25. The C_{max} for OM 10, 20, and 40mg doses increased in a slightly less than dose-proportional manner; considered to be not clinically significant. Dose-proportionality of AM was demonstrated as the 90% CI for dose-normalized parameters were within the 80–125% range. Mean terminal elimination half-life of OM (10 to 40mg) and AM (5 to 10mg) ranged from 14.0-15.1 h and 48.4-51.6 h respectively. OM 10, 20 or 40mg was well tolerated when given in fixed-dose combination with either AM 5 or 10mg. Most TEAEs were of mild severity and none considered treatment-related. There were no serious AEs. In conclusion, the exposure of OM and AM for the fixed-dose combinations increased in a dose-proportional manner.

Table

PK Parameters*	**OM dose**			**AM dose**		
	40mg [A and D] (n=59)	20mg [B and E] (n=54-57)	10mg [C and F] (n=58)		10mg [A,C,E] (n=87)	5mg [B,D,F] (n=87)
AUC_{0-t} (ng·h/mL)	6006.4	3512.4	1885.0	AUC_{0-t} (ng·h/mL)	385.8†	172.5
$AUC_{0-\infty}$ (ng·h/mL)	6096.2**	3573.8	1921.0	$AUC_{0-\infty}$ (ng·h/mL)	455.0†	200.3
C_{max} (ng/mL)	928.2	574.9	337.2	C_{max} (ng/mL)	7.7	3.6
*Arithmetic means are presented;**n=58; †n=86						

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LOW AND HIGH DOSES OF A FIXED-DOSE COMBINATION OF OLMESARTAM MEDOXOMIL (OLM) AND AMLODIPINE BESYLATE (AML) ARE BIOEQUIVALENT TO FREE COMBINATION OF THE AGENTS

Shashank Rohatagi, PhD[1] ;Stephen Haworth, MD[1]; Daniel E. Salazar, PhD[1]; Reinilde Heyrman, MD[1]; Mohinder Singh Bathala, PhD[1]; James Lee, PhD[1] Robert Noveck, MD[2]

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Two or more antihypertensive agents from different pharmacologic classes may be needed to reach a target BP of <140/90 mmHg in a majority of patients. The use of a fixed-dose combination such as the angiotensin receptor blocker OLM and the calcium channel blocker AML provides increased BP-lowering efficacy with good tolerability and ease of administration. The bioequivalence under fasting conditions of a fixed-dose combination of OLM and AML in low (OLM/AML 10/5mg) and high (OLM/AML 40/10mg) doses to that of the drugs coadministered separately was investigated in 2 cohorts of a randomized, open-label, 2-way crossover single-dose study in healthy subjects (n=60). Noncompartmental analyses showed the bioavailability of both OLM and AML after administration of the fixed-dose combination (Test) was similar to that of the agents coadministered separately (Reference), at both the low and high doses (Table). Mean $t_{1/2}$ for the low dose Test and Reference treatments were 14.3 and 13.6 hrs and for the high dose 15.6 and 17.3 hrs, respectively. Overall, treatment emergent adverse events (TEAEs) were mild; none were considered definitely or probably drug-related and the most common was headache. In conclusion, a single fixed-dose combination tablet of OLM/AML 10mg/5mg or 40mg/10mg was well tolerated and is bioequivalent to coadministration of single doses of OLM and AML under fasted conditions in healthy subjects.

Table

	Geometric LSM ratio (%) [Test/Reference]	90%CI (%)
Low dose (n=30)		
OM		
AUC_{0-t}	107.6	99.7, 116.1*
$AUC_{0-\infty}$ †	107.4	99.4, 116.0*
C_{max}	114.3	106.6, 122.5*
AM		
AUC_{0-t}	101.6	99.1, 104.2*
$AUC_{0-\infty}$	101.6	99.0, 104.3*
C_{max}	99.0	95.7, 102.5*
High dose (n=29)		
OM		
AUC_{0-t}	112.1	103.3, 121.6*
$AUC_{0-\infty}$ ‡	113.5	104.7, 123.0*
C_{max}	109.7	101.8, 118.3*
AM		
AUC_{0-t}	101.6	97.3, 106.2*
$AUC_{0-\infty}$	101.2	96.6, 106.0*
C_{max}	108.3	103.2, 113.6*
*Criteria for bioequivalence, i.e., 90%CI for the ratio of geometric LSM to be within 80.0 to 125.0%, were met		
LSM=least squares mean, †n=29, ‡n=27		

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Lack of Pharmacokinetic (PK) Drug Interaction Between Olmesartan Medoxomil (OM) and Amlodipine Besylate (AM) During Coadministration

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The majority of hypertensive patients require multiple drug regimens to achieve blood pressure (BP) goal. The angiotensin receptor blocker OM and the calcium channel blocker AM are each efficacious monotherapies and combining these agents adheres to JNC 7 guidelines for using combination therapies with complementary mechanisms of action. The PK interaction between these agents was investigated in an open-label, multiple-dose, 3-way crossover study in healthy subjects under fasting conditions. Subjects were assigned randomly to receive 1 of the following 10-day regimens on 3 occasions (each regimen separated by ≥21 days): treatment A - OM 40mg/d; treatment B - AM 10mg/d and treatment C - OM 40mg/d + AM 10mg/d. Noncompartmental, steady-state (day 10) PK parameters of OM following treatments A and C and of AM following treatments B and C are shown. [table1] All dosing regimens were well tolerated. There was no significant PK interaction between OM and AM. The 90% CIs for the ratio of geometric least squares mean for $AUC_{0-\tau}$ and C_{max} of OM and AM were within the 80.0-125.0% limit (combined treatment vs each monotherapy). Coadministration had no effect on the $t_{½}$ of either agent. The tolerability profile of combination therapy was similar to that of each monotherapy. There were no serious AEs or AE-related discontinuations. Most TEAEs were mild; the most frequent was headache (n=10/24). Drug-related AEs occurred in 5 subjects during combination therapy, and in 7 subjects with each monotherapy. In conclusion, coadministration of OM and AM did not affect the rate or extent of exposure of OM or AM and was well tolerated.

	OLM			**AML**		
PK parameters (mean)	**Treatment A n=23**	**Treatment C n=24**	**C/A ratio of geometric LSM (%) (90%CI)**	**Treatment B n=23**	**Treatment C n=24**	**C/B ratio of geometric LSM (%) (90%CI)**
AUC_{τ} (ng·h/mL)	6793.9	6890.9	101.1 (93.5, 109.4)	359.2	388.7	107.7 (100.1, 115.9
C_{max} (ng/mL)	1083.8	1038.1	95.2 (87.2, 103.9)	19.8	20.1	100.7 (91.3, 111.1)
t_{max} (h)[1]	1.5 (1.00, 2.52)	2.0 (1.02, 2.98)		8.00 (5.00, 14.00)	8.0 (0.0, 16.1)	
$t_{½}$ (h)	13.7	13.48		51.2	50.6	

[1]**Median (min, max) values presented**

C. EVIDENCE TABLE SPREADSHEETS (NOTED ABOVE) OF ALL PUBLISHED AND UNPUBLISHED TRIALS:

Study No. and Study Dates	Study Design/ Sample Size/Treatments	Inclusion & Exclusion Criteria	Endpoints/Results
CS-8663-A-U301 A randomized, double-blind, placebo-controlled, factorial study evaluating the efficacy and safety of co-administration of olmesartan medoxomil plus amlodipine compared to monotherapy in patients with mild to severe hypertension. (Data on File 2007, Daiichi Sankyo, Inc.) Q2 2005 – Q1 2006	**Design**: Randomized Double-blind Placebo-Controlled Multi-center Parallel-group factorial trial (Period II), 8 Weeks **Patient type and Sample Size** Mild to severe hypertension N= 1940 **Treatment Arms** Placebo OM 10 mg OM 20 mg OM 40 mg AML 5 mg AML 10 mg AML 5 mg + OM 10 mg AML 5 mg + OM 20 mg AML 5 mg + OM 40 mg AML 10 mg + OM 10 mg AML 10 mg + OM 20 mg or AML 10 mg + OM 40 mg *Subgroup Analyses of Age (<65 vs ≥ 65 years old); Diabetes Status; and Race (Black vs Non-Black) on ITT*	**Inclusion:** • Male or female patients 18 yrs and older • Female patients had to have a negative urine pregnancy test at screening, not lactating, and either post-menopausal for 1 year, surgically sterile, or using effective contraceptive methods • Mean SeDBP of ≥ 95 mm Hg and ≤ 120 mmHg by Visit 2 or 2.1 (pre-randomization) and Visit 3 (randomization) • Mean difference in SeDBP between the pre-randomization visit and randomization of ≤ 10 mm Hg **Exclusion:** • SeDBP > 120 mm Hg • Uncontrolled Type 1 or Type 2 DM defined as $HbA1_c$ > 9.0% • History of heart failure	**Primary** • Mean Change in SeDBP from baseline to Week 8 with LOCF – Intent to Treat o Each active treatment group had a statistically significant mean reduction in SeDBP from baseline to Week 8 with LOCF (p<0.0001) o Mean reductions in SeDBP were significantly greater in the combination therapy groups compared with the respective monotherapy groups. In the combination groups with AML 5 mg and 10 mg, increasing doses of OM (10 mg, 20 mg, and 40 mg) resulted in greater reductions in SeDBP. o Overall, the greatest reductions in seated diastolic blood pressure occurred in the group treated with OM 40 mg + AML 10 mg (-19.0 mm Hg) followed by the group treated with OM 20 mg + AML 10 mg (-17.0 mmHg). **Secondary** • Mean Change in SeSBP from baseline to Week 8 with LOCF – Intent to Treat o Each active treatment group had a statistically significant mean reduction in SeSBP from baseline to Week 8 with LOCF (p<0.0001) o Mean reductions in SeSBP were significantly greater in the combination therapy groups compared with the respective monotherapy groups. o Overall, the greatest reductions in seated systolic blood pressure occurred in the group treated with OM 40 mg + AML 10 mg (-30.1 mm Hg) followed by the group treated with OM 20 mg + AML 10 mg (-29.2 mm Hg).

CONTINUED - EVIDENCE TABLE SPREADSHEETS (NOTED ABOVE) OF ALL PUBLISHED AND UNPUBLISHED TRIALS

Study No. and Study Dates	Study Design/ Sample Size/Treatments	Inclusion & Exclusion Criteria	Endpoints/Results
		• History of MI, percutaneous transluminal coronary revascularization, coronary artery bypass graft, and/or unstable angina within the past 6 months • Hypertensive encephalopathy, stroke, or TIA within the past 6 months • History of secondary hypertension • Evidence of symptomatic resting bradycardia, hemodynamically significant cardiac valvular disease, and liver disease • Presence of heart block greater than 1st-degree SA block, chronic atrial fibrillation, or flutter • Uncorrected coarctation of the aorta, bilateral RAS, or unilateral RAS in a solitary kidney	• Change in SeDBP and SeSBP from Baseline to Weeks 2, 4, 6, and 8 without LOCF o Analysis results for the mean change in SeDBP and SeSBP from baseline to Week 2, Week 4, Week 6 and Week 8 without LOCF for the ITT population were similar to the results observed at Week 8 with LOCF. o For all active treatment groups, most of the mean reduction in SeDBP and SeSBP occurred from baseline to Week 2, which plateaued by Week 4 • Blood Pressure Goals o The percentage of patients achieving their blood pressure goals by Week 8 with LOCF ranged from 20.0% to 36.3% for the groups treated with monotherapy compared with 35.0% to 53.2% for the groups treated with combination therapy. o Approximately 50% of patients treated with one of the higher dose combination therapies (i.e., AML 10mg + OM 10 mg, AML 10 mg + OM 20 mg, AML 5 mg + OM 40 mg, and AML 10 mg + OM 40 mg) reached their blood pressure goal by Week 8 with LOCF Subgroup analyses were conducted on the ITT population for age (<65 vs ≥ 65 years old); diabetes status; and race (Black vs Non-Black). For each analyses, all active treatment arms had a statistically significant mean reduction in SeDBP and SeSBP from baseline. Combination therapy versus monotherapy resulted in significantly greater reductions in mean BP for those <65 yo, patients without diabetes, and non-Black patients, in each of the respective subgroups analyzed. However, for the comparative subgroups (≥ 65 yo, patients with diabetes, and Black patients), the results were not consistent (see pages 26 - 33).

CONTINUED - EVIDENCE TABLE SPREADSHEETS (NOTED ABOVE) OF ALL PUBLISHED AND UNPUBLISHED TRIALS

<table>
<tr><th>Study No. and Study Dates</th><th>Study Design/ Sample Size/Treatments</th><th>Inclusion & Exclusion Criteria</th><th>Endpoints/Results</th></tr>
<tr>
<td>CS-8663-A-U301
A randomized, double-blind, placebo-controlled, factorial study evaluating the efficacy and safety of co-administration of olmesartan medoxomil plus amlodipine compared to monotherapy in patients with mild to severe hypertension. (Data on File 2007, Daiichi Sankyo, Inc.)

Q2 2005 – Q1 2007

(Phase III, US Study)</td>
<td>Design:
Open-Label Treatment Week 8 to Week 52
(Period III)
(Results from the double-blind period (Period II – Day 1 to Week 8) are above)

Sample Size: N=1684 (these patients completed Period II and entered Period III)

Treatments:
Treat-to-goal
All patients started on:
o AML 5 mg + OM 40 mg
Titrated if goal of <140/90 mm Hg or <130/80 mm Hg for those patients with DM was not achieved:
o AML 10 mg + OM 40 mg
o AML 10 mg + OM 40 mg + HCTZ 12.5 mg
o AML 10 mg + OM 40 mg + HCTZ 25 mg

If SeDBP was >120 mm Hg while on maximal therapy, the patient was discontinued from the study</td>
<td>Inclusion:
• Male or female patients 18 yrs and older
• Female patients had to have a negative urine pregnancy test at screening, not lactating, and either post-menopausal for 1 year, surgically sterile, or using effective contraceptive methods
• Mean SeDBP of ≥ 95 mm Hg and ≤ 120 mm Hg by Visit 2 or 2.1 (pre-randomization) and Visit 3 (randomization)
• Mean difference in SeDBP between the pre-randomization visit and randomization of ≤ 10 mm Hg

Exclusion:
• SeDBP > 120 mm Hg
• Uncontrolled Type 1 or Type 2 DM defined as $HbA1_c$ > 9.0%
• History of heart failure
• History of MI, percutaneous transluminal coronary revascularization, coronary artery bypass graft, and/or unstable angina within the past 6 months</td>
<td><u>Mean SeDBP and SeSBP and percentage of patients achieving blood pressure goals by week for each treatment</u>

Mean SeDBP and SeSBP and % of Patients Reaching BP Goal at Week 52 or Early Termination and by Dosing Regimen

<table>
<tr><th>Treatment (mgs)</th><th>n</th><th>Mean SeDBP (mm Hg)</th><th>Mean SeSBP (mm Hg)</th><th>% of Subjects Reaching BP Goal*</th></tr>
<tr><td>AML 5/OM 40</td><td>525</td><td>81.0</td><td>127.6</td><td>80.0</td></tr>
<tr><td>AML 10/OM 40</td><td>378</td><td>82.4</td><td>130.9</td><td>70.6</td></tr>
<tr><td>AML 10/OM 40 + HCTZ 12.5</td><td>287</td><td>81.0</td><td>130.7</td><td>66.6</td></tr>
<tr><td>AML 10/OM 40 + HCTZ 25</td><td>419</td><td>83.4</td><td>136.8</td><td>46.3</td></tr>
<tr><td>Other**</td><td>63</td><td>79.4</td><td>126.2</td><td>68.3%</td></tr>
</table>
*<140/90 mm Hg or <130/80 for patients with diabetes
** Despite the treatment algorithm presented, some investigators elected for a variety of reasons to use alternative antihypertensive medications

• From the mean baseline BP of 163.6/101.5 mm Hg, BP reductions were observed across all combination treatment regimens to Week 52. Also, each titration to a more intensive treatment regimen resulted in additional mean reductions of SeBP.

• The groups of patients who required titration of the amlodipine dose or the addition of HCTZ were more severe hypertensive patients and/or were more resistant to the antihypertensive effects of treatment</td>
</tr>
</table>

CONTINUED - EVIDENCE TABLE SPREADSHEETS (NOTED ABOVE) OF ALL PUBLISHED AND UNPUBLISHED TRIALS

Study No. and Study Dates	Study Design/ Sample Size/Treatments	Inclusion & Exclusion Criteria	Endpoints/Results
		• Hypertensive encephalopathy, stroke, or TIA within the past 6 months • History of secondary hypertension • Evidence of symptomatic resting bradycardia, hemodynamically significant cardiac valvular disease, and liver disease • Presence of heart block greater than 1st-degree SA block, chronic atrial fibrillation, or flutter • Uncorrected coarctation of the aorta, bilateral RAS, or unilateral RAS in a solitary kidney	• As patients were titrated to more intensive treatment regimens, an overall greater percentage of patients reached their BP treatment goal

CONTINUED - EVIDENCE TABLE SPREADSHEETS (NOTED ABOVE) OF ALL PUBLISHED AND UNPUBLISHED TRIALS

Study No. and Study Dates	Study Design/ Sample Size/Treatments	Inclusion & Exclusion Criteria	Endpoints/Results
CS-8663-A-E302 Efficacy and safety of Amlodipine used as add-on therapy in moderately to severely hypertensive patients not adequately controlled by olmesartan medoxomil 20 mg monotherapy (Data on File 2007, Daiichi Sankyo, Inc.) Q4 2005 – Q4 2006 (Phase III, European Study)	**Design**: 8 week open-label monotherapy (Period I) and 8 week randomized double-blind treatment (Period II); Parallel-group Multi-national Multi-center **Patient Type and Sample Size**: Moderate to Severe hypertension or uncontrolled on OM monotherapy Period I, n = 722 Period II, n=538 **Treatment Arms**: **Period I**: OM 20 mg (all patients received monotherapy, n = 722) **Period II**: Non-responders from Period I randomized to: • Placebo + OM 20 mg • AML 5 mg + OM 20 mg • AML 10 mg + OM 20 mg *(Non-responder defined as mean trough SeBP ≥ 140/90, mean 24-hour DBP ≥ 80 mm Hg, and at least 30% of daytime DBP readings >85 mm Hg)*	**Inclusion:** • Male or female patients 18 yrs or older • History of moderate to severe hypertension (SBP ≥ 160 mm Hg & DBP ≥ 100 mm Hg; mean 24 hours DBP of ≥ 84 mm Hg at Visit 2; and at least 30% of daytime DBP readings > 90 mm Hg • Patients treated with OM 20 or 40 mg had to have a previous diagnosis of moderate to severe hypertension, were uncontrolled on monotherapy (≥ 140/90 mm Hg), mean 24 hour DBP of ≥ 80 mm Hg at Visit 2; and at least 30% of daytime DBP readings > 85 mm Hg **Exclusion** • Mean SeDBP > 115 mm Hg • Mean SeSBP > 200 mm Hg • Mean 24-hour DBP as assessed by 24 hour ABPM>104 mmHg • Bradycardia (<50 beats/min)	**Primary** • Mean change from baseline (Week 8) to Week 16 (end of double-blind treatment period) in trough SeDBP using LOCF o Combination arms (AML 5/OM 20 & AML 10/OM 20) reduced the mean SeDBP to a significantly greater extent than treatment with OM 20 + placebo; -2.7 mmHg for AML 5/OM 20 (p=0.0006 vs. monotx) and -3.2 mmHg for AML 10/OM 20 (p< 0.0001 vs. monotx) **Secondary** • Mean change from baseline (Week 8) to Week 16 (end of double-blind) in trough SeSBP using LOCF o Combination arms (AML 5/OM 20 & AML 10/OM 20) resulted in statistically significant reductions in adjusted mean sitting SBP when compared with OM 20 mg + placebo therapy: -5.8 mm Hg for AML 5 mg + OM 20 mg (p<0.0001) and -6.4 mmHg for AML 10 mg + OM 20 mg (p<0.0001) • Mean change from baseline (Week 8) to Week 16 (end of double-blind) in daytime, nighttime, and 24-hour DBP and SBP assessed by 24-hour ABPM o Combination arms resulted in statistically significant reductions in 24-hour, daytime, and nighttime adjusted mean changes for DBP and SBP when compared with monotherapy • Mean change from baseline (Week 8) to Week 12 in trough SeDBP & SeSBP w/o LOCF o The adjusted mean change in SeDBP at Week 12 for patients treated with OM 20 mg + AML 10 mg combination therapy (-2.8 mmHg) was statistically significant when compared to OM 20 mg + placebo therapy (p=0.0002). The adjusted mean change in sitting DBP at Week 12 for patients treated with OM 20 mg + AML 5 mg was -0.9 mmHg when compared to OM 20 mg + placebo therapy (p=0.3703)

CONTINUED - EVIDENCE TABLE SPREADSHEETS (NOTED ABOVE) OF ALL PUBLISHED AND UNPUBLISHED TRIALS

Study No. and Study Dates	Study Design/ Sample Size/Treatments	Inclusion & Exclusion Criteria	Endpoints/Results
			o Adjusted mean change in SeSBP at Week 12: The differences from OM 20 mg + placebo in adjusted mean change in SeSBP for both the OM 20 mg + AML 5 mg treatment group (-2.9 mm Hg; p=0.0220) and the OM 20 mg + AML 10 mg treatment group (-6.3 mm Hg; p<0.0001) were statistically significant. o The difference in BP reduction between the OM 20mg + placebo arm and combination arms was greater in the OM 20 mg + AML 10 mg arm, compared to the OM 20 mg + AML 5 mg arm. However, with time, the differences between the 2 combinations were narrowed by week 16. • Blood Pressure Goals Compared to patients treated with OM 20 mg + placebo (28.5% achieving goal), the percentage of patients achieving BP goal at week 16 with LOCF was significantly higher in the OM 20 mg + AML 5 mg treatment group (44.5%; p=0.0011) and in the OM 20 mg + AML 10 mg treatment group (45.8%; p=0.0004)

CONTINUED - EVIDENCE TABLE SPREADSHEETS (NOTED ABOVE) OF ALL PUBLISHED AND UNPUBLISHED TRIALS

Study No. and Study Dates	Study Design/ Sample Size/Treatments	Inclusion & Exclusion Criteria	Endpoints/Results
CS-8663-A-E303 Add-on Study of olmesartan medoxomil in patients with moderate to severe hypertension not achieving target blood pressure on amlodipine 5mg alone (Data on File 2007, Daiichi Sankyo, Inc.) Q4 2005 – Q4 2006 (to Week 34) Phase III, European Study	**Design:** 52 week study consisting of 4 periods: Period 1: Open-label monotherapy Period II: Double-blind treatment Period III: Double-blind treatment with dose up-titration Period IV: Open-label Combination Treatment Randomized Parallel-group Multi-national Multi-center **Patient type and Sample Size** Moderate to severe hypertension (≥160/100) or uncontrolled on AML monotherapy (≥140/90) Period 1: n=1017 Period 2: n=755 Period 3: n=706 Period 4: n=677 Treatment Arms: Period I: AML 5 mg (8 weeks) Period II: Non-responders from Period I randomized to (8 weeks): • AML 5 mg + placebo • AML 5 mg + OM 10 mg • AML 5 mg + OM 20 mg • AML 5 mg + OM 40 mg	**Inclusion:** • Male or female patients 18 yrs or older • History of moderate to severe hypertension (SBP ≥ 160 mm Hg & DBP ≥ 100 mm Hg; mean 24 hours DBP of ≥ 84 mm Hg at Visit 2; and at least 30% of daytime DBP readings > 90 mm Hg • Patients treated with AML 5 mg or 10 mg had to have a previous diagnosis of moderate to severe hypertension, were uncontrolled on monotherapy (≥ 140/90 mm Hg), mean 24 hour DBP of ≥ 80 mm Hg at Visit 2; and at least 30% of daytime DBP readings > 85 mm Hg **Exclusion** • Mean SeDBP > 115 mm Hg • Mean SeSBP > 200 mm Hg • Mean 24-hour DBP as assessed by 24 hour ABPM>104 mm Hg • Bradycardia (<50 beats/min)	**Primary** • Mean change in trough sitting DBP from baseline (Week 8) to Week 16 – Period II o Combination arms (AML 5/OM 10, AML 5/OM 20, & AML 5/OM 40) reduced the mean SeDBP to a significantly greater extent than treatment with AML 5mg + placebo; -2.0 mm Hg for AML 5/OM 10 (p=0.0207 vs. monotx); -3.7 mm Hg for AML 5/OM 20 (p=<0.0001 vs. monotx); and -3.8 mm Hg for AML 5/OM 40 (p< 0.0001 vs. monotx) **Secondary** • Mean change in trough SeSBP from baseline (Week 8) to Week 16 – Period II o Compared with placebo + AML 5 mg, treatment with AML + OM resulted in statistically significant reductions in sitting SBP at Week 16 with LOCF (-3.5 mm Hg, p=0.0103 for OM 10 mg + AML 5 mg; -5.8 mm Hg, p<0.0001 for OM 20 mg + AML 5 mg; and -7.1 mm Hg, p<0.0001 for OM 40 mg + AML 5 mg) • Mean change in trough SeDBP and SeSBP from baseline to Week 12, from Week 16 to Week 20 and 24; and at Week 34 o Combination arms demonstrated significantly larger mean reductions in SeDBP and SeSBP than AML 5 mg + placebo at Week 12 and Week 16; the DBP lowering effect of AML 5/OM 40 occurred earlier than that of AML 5/OM 20, however at Week 16 both arms had numerically larger mean reductions in SeDBP than AML 5/OM 10 o Mean change in trough SeDBP and SeSBP from Week 16 to Week 20 and 24 was not meaningful for patients not titrated; however, for those who were titrated further mean reductions in SeDBP and SeSBP occurred o At Week 34, mean SeBP for the AML 5/OM 40 arm was 132.2/83.6 mm Hg; for the AML 10/OM 40 arm was 143/90.3 mm Hg; for the AML 10/OM 40/HCTZ 12.5 arm was 147.6/89.3; and for the AML 10/OM 40/HCTZ 25 arm was 155.3/92 mm Hg

CONTINUED EVIDENCE TABLE SPREADSHEETS (NOTED ABOVE) OF ALL PUBLISHED AND UNPUBLISHED TRIALS

Study No. and Study Dates	Study Design/ Sample Size/Treatments	Inclusion & Exclusion Criteria	Endpoints/Results
	(Non-responder defined as mean trough SeBP ≥ 140/90, mean 24-hour DBP ≥ 80 mm Hg, and at least 30% of daytime DBP readings >85 mm Hg) Period III: Patients uncontrolled in Period II had doses titrated (all others continued on assigned treatment regimen) (8 weeks): • AML 5 mg + placebo to AML 5 mg + OM 20 mg • AML 5 mg + OM 10 mg to AML 5 mg + OM 20 mg • AML 5 mg + OM 20 mg to AML 5 mg + OM 40 mg • AML 5 mg + OM 40 mg to AML 10 mg + OM 40 mg Period IV: Open-label Combination Treatment (28 weeks): • Initial treatment with AML 5 mg + OM 40 mg • Then: AML 10 mg + OM 40 mg (if needed) • Then: AML 10 mg + OM 40 mg + HCTZ 12.5 mg (if needed) • Then: AML 10 mg + OM 40 mg + HCTZ 12.5 mg (if needed)		• Mean change from baseline (Week 8) to Week 16 (end of double-blind) and from Week 16 to Week 24 in daytime, nighttime, and 24-hour DBP and SBP assessed by 24-hour ABPM o Combination arms resulted in statistically significant reductions in 24-hour, daytime & nighttime adjusted mean changes for DBP and SBP when compared with monotherapy **Blood Pressure Goals** • After double-blind treatment, compared with AML 5 mg + placebo, treatment with the combinations resulted in a statistically significantly higher proportion of patients who reached BP goal at Week 16 with LOCF (50.5% - AML 5/OM 40; 53.5% - AML 5/OM 20; and 39.2% - AML 5/OM 10; versus 29.9% - AML 5/placebo) • In Period III, for patients who remained on their randomized treatment regimen, the proportion who reached BP goal at Week 24 with LOCF was higher with AML + OM treatment than with AML 5mg + placebo. For patients whose dose regimen was titrated, successively higher proportions reached BP goal with each increase in dose combination of AML + OM.

3 SUPPORTING INFORMATION

3.1 REFERENCES

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